UNIVERSITY OF LONDON
MEDICAL LIBRARY

Medical Deposit (8)

SHL
WITHDRAWN

W. Roy. Med. Chir. Soc.

Digitized by the Internet Archive
in 2026

https://archive.org/details/proceedings-of-the-association-of-american-physicians_1903_18

2nd Copy

TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

EIGHTEENTH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 12, 13 AND 14, 1903.

VOLUME XVIII.

PHILADELPHIA:
PRINTED FOR THE ASSOCIATION.
1903.

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings

DORNAN, PRINTER,
701-709 ARCH STREET,
PHILADELPHIA.

CONTENTS.

	PAGE
List of Officers for the year 1903–1904	vii
List of Officers from organization to the present time	viii
List of Members	ix
List of Honorary Members	xiii
List of Deceased Members	xiv
Constitution	xv
Minutes of the Eighteenth Annual Meeting	xix

PAPERS.

Address of the President. By JAMES STEWART, M.D.	1
Bathycardia. By E. G. JANEWAY, M.D.	5
The Transmission of Bovine Tuberculosis by Milk, with a Tabulation of Eighty-six Cases. By GEORGE M. KOBER, M.D.	9
On the Production of Specific Cytolytic Sera for Thyroid and Parathyroid, with Observations on the Physiology and Pathology of the Parathyroid Gland, Especially in its Relation to Exophthalmic Goiter. By W. G. MACCALLUM, M.D.	35
Paroxysmal Hematinuria. (Hémoglobinurie a Frigore.) By W. GILMAN THOMPSON, M.D.	54
Report of a Case of Pulsating Empyema Necessitatis, with Three Strongly Pulsating Tumors. By FREDERICK P. HENRY, M.D.	71
The Third and Final Report of a Case of Presystolic Mitral Murmur, Complicating Pregnancy, etc., with Exhibition of Specimen, Showing Triple Valvular Lesion. By JAMES TYSON, M.D.	81
Intussusception, with Report of a Case of Recovery after the Extrusion of Eleven Inches of Intestine. By NORMAN BRIDGE, M.D.	85
The Use of the X-rays in the Treatment of Diseases of the Skin, of New-growths, of the Glandular System, and of Other Diseases, and as a Means of Relieving Pain. By FRANCIS H. WILLIAMS, M.D.	89
Artificial Immunity in Experimental Tuberculosis. By E. L. TRUDEAU, M.D.	97
Studies in Mammalian Tubercle Bacilli III. Description of a Bovine Bacillus from the Human Body. A Culture Test for Distinguishing the Human from the Bovine Type of Bacilli. By THEOBALD SMITH, M.D.	109

PAGE

Experimental Studies on the Eosinophilia of Trichinosis. A Preliminary Report. By HERBERT U. WILLIAMS, M.D., and CHARLES A. BENTZ, M.D. 152

The Clinical Associations and Significance of the Cardiopulmonary Murmur. By JAMES J. PUTNAM, M.D. 157

Typhoid Fever: An Analysis of Seven Hundred and Seventeen Cases. By JOHN MCCRAE, B.A., M.B. (Tor.) 165

A Case of Gastric Syphilis. By H. A. LAFLEUR, M.D. 176

Infantile Scorbutus. By THOMAS MORGAN ROTCH, M.D. 180

Dermatomyositis. By F. FORCHHEIMER, M.D. 184

Studies upon the Capsule of the Kidney. By HAVEN EMERSON, M.D. Presented by S. J. MELTZER, M.D. 192

Skin Lesions Associated with Rapid Growth of Long Bones—Lineæ Albicantes (Les Vergetures de Croissance, Jules Comby). By W. P. NORTHRUP, M.D. 197

Two Cases of General Gonococcal Peritonitis in Young Girls under Puberty, One Simulating Appendicitis: Operated. By W. P. NORTHRUP, M.D. 202

The Relation of Chronic Enlargement of the Spleen to Anemia in Infancy. By JOHN LOVETT MORSE, M.D. 207

Sudden Death and Unexpected Death in Early Life, with Especial Reference to the So-called Thymus Death. By J. P. CROZER GRIFFITH, M.D. 235

Note on Typhoid Fever and Scarlet Fever, with Special Reference to the Diagnostic Value of Blood Cultures. By LUDVIG HEKTOEN, M.D. 254

The Influence of the Different Varieties of Fat on the Formation and Excretion of Acetone. By E. P. JOSLIN, M.D. 260

Tuberculosis of the Tonsils and the Tonsils as a Portal of Tuberculous Infection. By HENRY KOPLIP, M.D. 262

A Case of Extreme Malformation of the Heart. By JAMES HOMER WRIGHT, M.D., and ARTHUR K. DRAKE, M.D. 272

The Adrenal Gland and its Active Principle in Their Relations to Cytolysins and Antitoxin Production. By A. C. ABBOTT, M.D. 275

Chronic Cyanosis, with Polycythemia and Enlarged Spleen: A New Clinical Entity. By WILLIAM OSLER, M.D. 299

Post-typhoid Sepsis. By FRANCIS DELAFIELD, M.D. 326

A Case of Pulsating Serous Pleural Effusion. By ALEXANDER MCPHEDRAN, M.B. 334

A Case of Massive Hemorrhagic Infarction of the Lung Due to Pulmonary Endarteritis and Thrombosis. By A. MCPHEDRAN, M.B., and J. J. MACKENZIE, B.A., M.B. 337

Report of a Case of Decapsulation of the Kidney (Edebohls' Operation) for Chronic Parenchymatous Nephritis. By JAMES TYSON, M.D., and CHARLES H. FRAZIER, M.D. 347

PAGE

A Note on Autolysis in Lobar and Unresolved Pneumonia. By Simon Flexner, M.D. 359

A Further Report on the Study of Bacterial Cells. By Victor C. Vaughan, M.D. 365

Treatment of Migraine. By B. K. Rachford 369

A Case of Chronic Lymphatic Leukemia without Enlargement of the Lymph Nodes. By George Blumer, M.D., and Hermon C. Gordinier, M.D. 378

A Preliminary Note on Some Experiments to Determine Whether Alcohol Does Good in Infections by Increasing the Bacteriolytic Power of the Blood. By H. A. Hare, M.D. 391

Studies on the Action of Alcohol in Disease, Especially upon the Circulation. By Richard C. Cabot, M.D. 402

Actinomycosis of the Central Nervous System, with the Report of a Case Due to an Unidentified Member of the Actinomyces Group. By William Travis Howard, Jr., M.D. 427

Acute Bulbar Paralysis Due to Hemorrhage and Softening of the Pons and Medulla. With Reports of Cases and Autopsies. By Charles L. Dana, A.M., M.D. 446

Acute Lymphocytic Leukemia, with Reference to its Myelogenous Origin. By A. O. J. Kelly, A.M., M.D. 481

A Clinical and Pathological Study of Two Cases of Splenic Anemia, with Early and Late Stages of Cirrhosis (Early and Late Stages of Banti's Disease). By George Dock, M.D., and Aldred Scott Warthin, M.D. 522

An Experimental Study of Nephrotoxins. By Richard M. Pearce, M.D. 557

On the Visceral Manifestations of the Erythema Group of Skin Diseases. (Third Paper.) By William Osler, M.D. 599

Primary Cancer of the Lungs. By J. H. Musser, M.D. 625

A Description of the Brains and Spinal Cords of Two Brothers Dead of Hereditary Ataxia. Cases XVIII. and XX. of the Series in the Family Described by Dr. Sanger Brown. By Lewellys F. Barker, M.D. 637

ASSOCIATION OF AMERICAN PHYSICIANS

OFFICERS FOR THE YEAR 1903–1904.

PRESIDENT.

WM. T. COUNCILMAN, M.D.

VICE–PRESIDENT.

E. L. TRUDEAU, M.D.

SECRETARY.

HENRY HUN, M.D.

RECORDER.

SOLOMON SOLIS COHEN, M.D.

TREASURER.

J. P. CROZER GRIFFITH, M.D.

COUNCILLORS.

FRANK BILLINGS, M.D.
FRANCIS P. KINNICUTT, M.D.
CHARLES G. STOCKTON, M.D.
V. C. VAUGHAN, M.D.
GEORGE M. KOBER, M.D.

REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.

WILLIAM OSLER, M.D.

ALTERNATE REPRESENTATIVE.

FRANCIS H. WILLIAMS, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME.

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis Delafield.	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	Geo. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard.	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	Jas. C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	Jas. Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.

MEMBERS.

* Original Members.

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Station L, St. Charles Ave., Baltimore.
1894. Adami, J. George, Pathological Laboratory, McGill University, Montreal, Canada.
1896. Adler, Isaac, 12 East 60th St., New York.
*1886. Atkinson, I. E., 605 Cathedral St., Baltimore.
1899. Barker, L. F., University of Chicago, Chicago.
*1886. Baumgarten, G., 5227 Washington Boulevard, St. Louis.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 100 State St., Chicago.
1898. Blackader., A. D., 236 Mountain St., Montreal, Canada.
1901. Blumer, George, 247 State St., Albany, N. Y.
1892. Bolton, B. Meade, 4201 Maryland Ave., St. Louis.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1898. Brannan, John W., 11 West 12th St., New York.
1888. Bridge, Norman, 217 S. Broadway, Los Angeles, Cal.
1899. Cabot, R. C., 190 Marlborough St., Boston.
1889. Cary, Charles, 340 Delaware Ave., Buffalo, N. Y.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.
*1886. Councilman, Wm. T., 78 Bay State Road, Boston.
1897. Cushny, Arthur C., University of Michigan, Ann Arbor, Mich.
1894. Cutler, Elbridge G., 214 Beacon St., Boston.
1888. Dana, Charles L., 50 West 46th St., New York.
1888. Danforth, I. N., 905 West Monroe St., Chicago.
*1886. Delafield, Francis, 12 West 32d St., New York.
1893. Dock, George, 14 Cornwell Place, Ann Arbor, Mich.
1901. Dunham, E. K., 338 East 26th St., New York.
*1886. Edes, Robert T., 15 Greenough Ave., Jamaica Plain, Mass.
1901. Edwards, Arthur R., 103 State St., Chicago.
1899. Ely, John S., 60 Wall St., New Haven, Conn.

ELECTED

1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1895. Fischel, W. E., 2647 Washington Ave., St. Louis.
*1886. Fitz, Reginald H., 18 Arlington St., Boston.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, New York.
*1886. Forchheimer, F., 160 West 9th St., Cincinnati, Ohio.
1894. Fussell, M. Howard, 189 Green Lane, Manayunk, Philadelphia.
1903. Futcher, Thomas B., 3 West Franklin St., Baltimore.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1897. Hektoen, Ludwig, Rush Medical College, Chicago.
*1886. Henry, Frederick P., 1635 Locust St., Philadelphia.
1898. Herrick, James B., 200 Ashland Boulevard, Chicago.
1898. Herter, C. A., 819 Madison Ave., New York.
1900. Holt, L. E., 14 West 55th St., New York.
1901. Howard, Wm. T., Jr., 88 Dorchester Ave., Cleveland, Ohio.
*1886. Hun, Henry, 149 Washington Ave., Albany, N. Y.
1901. Jackson, Henry, 309 Marlborough St., Boston.
*1886. Jacobi, A., 19 East 47th St., New York.
1899. James, Walter B., 17 West 54th St., New York.
*1886. Janeway, E. G., 36 West 40th St., New York.
1902. Joslin, E. P., 517 Beacon St., Boston.
1902. Kelly, A. O. J., 1911 Pine St., Philadelphia.
*1886. Kinnicutt, Francis P., 39 East 35th St., New York.
1901. Kinyoun, J. J., U. S. Marine Hospital Corps, Detroit.
1902. Kober, Geo. M., 1600 T St., N. W., Washington, D. C.
1900. Koplik, Henry, 66 East 58th St., New York.
1895. Lafleur, Henri A., 58 University St., Montreal, Canada.
1890. Latimer, Thomas S., 211 West Monument St., Baltimore.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
*1886. Longstreth, Morris, 1416 Spruce St., Philadelphia.
1889. Loving, Starling, 229 East State St., Columbus, Ohio.
1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
1902. MacCallum, W. G., Johns Hopkins Hospital, Baltimore.
1898. Mallory, F. B., Department of Pathology, Harvard Medical School, Boston.
1903. Martin, Charles F., 33 Durocher St., Montreal.

ELECTED

1887. Meigs, Arthur V., 1322 Walnut St., Philadelphia.
1892. Meltzer, S. J., 166 West 126th St., New York.
1898. Mitchell, John K., 256 South 15th St., Philadelphia.
*1886. Mitchell, S. Weir, 1524 Walnut St., Philadelphia.
1901. Morse, John Lovett, 70 Bay State Road, Boston.
1887. Musser, John H., 1927 Chestnut St., Philadelphia.
1891. Northrup, W. P., 57 East 79th St., New York.
1900. Novy, F. G., University of Michigan, Ann Arbor, Mich.
1902. Opie, E. L., 1121 Madison Ave., Baltimore.
*1886. Osler, Wm., 1 West Franklin St., Baltimore.
1899. Park, Wm. H., 315 West 76th St., New York.
*1886. Peabody, Geo. L., 57 West 38th St., New York.
1898. Pfaff, Franz, 153 Huntington Ave., Boston.
1903. Preble, Robert B., 103 State St., Chicago.
1899. Prince, Morton, 458 Beacon St., Boston.
*1886. Prudden, T. Mitchell, 160 West 59th St., New York.
*1886. Putnam, James J., 106 Marlborough St., Boston.
1894. Rachford, B. K., 117 Broadway, Cincinnati.
*1886. Robinson, Beverley, 37 West 35th St., New York.
1893. Rotch, T. M., 197 Commonwealth Ave., Boston.
1898. Sachs, B., 21 East 65th St., New York.
1900. Sears, George G., 19 Marlborough St., Boston.
1900. Sewall, Henry, 23 Eighteenth Ave., Denver, Col.
*1886. Shattuck, Frederick C., 135 Marlborough St., Boston.
*1886. Shattuck, George B., 183 Beacon St., Boston.
*1886. Sinkler, Wharton, 1606 Walnut St., Philadelphia.
1902. Sippy, B. W., 103 State St., Chicago.
*1886. Smith, A. A., 40 West 47th St., New York.
1891. Smith, Andrew H., 18 East 46th St., New York.
1892. Smith, Theobald, South St., Forest Hills, Boston.
1887. Starr, M. Allen, 5 West 54th St., New York.
1898. Stengel, Alfred, 1811 Spruce St., Philadelphia.
*1886. Sternberg, George M., U. S. A., Surgeon-General's Office, Washington, D. C.
1896. Stewart, D. D., 1429 Walnut St., Philadelphia.
*1886. Stewart, James, 285 Mountain St., Montreal, Canada.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1899. Thacher, J. S., 33 West 39th St., New York.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1899. Thompson, W. Gilman, 34 East 31st St., New York.

ELECTED

1889. Thomson, Wm. H., 23 East 47th St., New York.
*1886. Trudeau, Edward L., Saranac Lake, Franklin Co., N. Y.
*1886. Tyson, James, 1506 Spruce St., Philadelphia.
1889. Vaughan, Victor C., University of Michigan, Ann Arbor, Mich.
1898. Vickery, Herman F., 263 Beacon St., Boston.
1889. Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.
*1886. Ward, Samuel B., 281 State St., Albany, N. Y.
1901. Warthin, Aldred S., University of Michigan, Ann Arbor, Mich.
*1886. Welch, Wm. H., 935 St. Paul St., Baltimore.
1898. Wesbrook, F. F., State Board of Health, Minneapolis, Minn.
*1886. Wilkins, George, 899 Dorchester St., Montreal, Canada.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
*1886. Wilson, James C., 1437 Walnut St., Philadelphia.
1898. Withington, Charles F., 35 Bay State Road, Boston.
*1886. Wood, Horatio, 1925 Chestnut St., Philadelphia.
1899. Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

HONORARY MEMBERS.

Elected Active Member.	Elected Honorary Member.	
1886.	1902.	Ball, A. Brayton, M.D., 42 W. 36th St., New York.
1886.	1887.	Billings, John S., M.D., Astor Library, Lafayette Place, New York.
1886.	1897.	Chew, Samuel C., M.D., 215 W. Lanvale St., Baltimore.
1886.	1899.	Dana, Israel T., M.D., 181 State St., Portland, Maine.
1890.	1902.	Fisk, S. A., M.D., Denver Club, Denver, Col.
1886.	1901.	Folsom, Charles F., M.D., 15 Marlborough St., Boston.
1886.	1900.	Guitéras, John, M.D., Havana, Cuba.
1886.	1902.	Hays, I. Minis, M.D., 268 S. 21st St., Philadelphia.
1890.	1902.	Hurd, H. M., M.D., Johns Hopkins Hospital, Baltimore.
1886.	1902.	Lyman, H. M., M.D., 220 Ashland Boulevard, Chicago.
1891.	1900.	Mason, A. Lawrence, M.D., 265 Clarendon St., Boston.
1886.	1897.	Miles, F. T., M.D., 514 Cathedral St., Baltimore.
1886.	1898.	Polk, Wm. M., M.D., 7 E. 36th St., New York.
1887.	1902.	Starr, Louis, M.D., 1818 S. Rittenhouse Square, Philadelphia.

DECEASED MEMBERS.

Date of Election.	
*1890.	Barker, Fordyce, M.D., New York.
*1886.	Bowditch, Henry I., M.D., Boston.
1886.	Bruen, Edward T., M.D., Philadelphia.
1886.	Busey, Samuel C., M.D., Washington, D. C.
*1886.	Clark, Alonzo, M.D., New York.
*1886.	Clymer, Meredith, M.D., New York.
1886.	Da Costa, J. M., M.D., Philadelphia.
1889.	Dabney, William C., M.D., University of Virginia.
*1886.	Dalton, John C., M.D., New York.
1886.	Donaldson, Frank, M.D., Baltimore.
1886.	Draper, William H., M.D., New York.
1886.	Formad, Henry F., M.D., Philadelphia.
1889.	Geddings, W. H., M.D., Aiken, S. C.
1886.	Graham, J. E., M.D., E. Toronto, Canada.
1886.	Howard, R. Palmer, M.D., Montreal, Canada.
1886.	Hudson, E. Darwin, Jr., M.D., New York.
1886.	Hutchinson, James H., M.D., Philadelphia.
1886.	Johnson, Hosmer A., M.D., Chicago.
1899.	Johnston, W. G., M.D., Montreal, Canada.
1886.	Johnston, W. W., M.D., Washington, D. C.
*1886.	Leidy, Joseph, M.D., Philadelphia.
1886.	Loomis, Alfred L., M.D., New York.
1886.	McBride, Thomas A., M.D., New York.
1890.	MacDonnell, R. P., M.D., Montreal, Canada.
*1886.	Metcalf, John T., M.D., Cold Spring, N. Y.
1886.	Minot, Francis, M.D., Boston.
1898.	Packard, Frederick A., M.D., Philadelphia.
1886.	Pepper, William, M.D., Philadelphia.
1888.	Prentiss, D. W., M.D., Washington, D. C.
1896.	Reed, Walter, M.D., Washington, D. C.
1887.	Reeves, James E., M.D., Chattanooga, Tenn.
*1886.	Rochester, Thomas F., M.D., Buffalo, N. Y.
1889.	Roosevelt, J. West, M.D., New York.
1886.	Ross, George, M.D., Montreal Canada.
1886.	Schmidt, H. D., M.D., New Orleans.
*1886.	Stillé, Alfred, M.D., Philadelphia.
1886.	Thacher, James K., M.D., New Haven, Conn.
1886.	Whittaker, James T., M.D., Cincinnati.

* Honorary Members.

ASSOCIATION

OF

AMERICAN PHYSICIANS.

CONSTITUTION

As Amended May 2, 1899.

Article I.

Object and Name.

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II.

Members.

The number of active members shall be limited to one hundred and twenty-five. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III.

Officers.

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually;

five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV.

Duty of Officers.

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V.

Council.

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI.

Meetings.

1. The Association shall hold an annual meeting in the City of Washington, D. C., at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. Authors of papers, and referees and co-referees who open a discussion shall not occupy more than thirty minutes each; and in the discussion following, the remarks of each speaker shall be limited to ten minutes.

5. The referees, co-referees, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII.

Quorum.

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum; and for altering the Constitution, twenty-five members shall be necessary.

Article VIII.

Election of Members.

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee, and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX.

Annual Dues.

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X.

Amendments to the Constitution.

Amendments to the Constitution must be proposed in writing by five members at an annual meeting and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendments; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

EIGHTEENTH ANNUAL MEETING,

Held at Washington, D. C., May 12, 13 and 14, 1903.

The following members were present during the meeting:

A. C. Abbott,
J. J. Abel,
J. Adler,
L. F. Barker,
H. M. Briggs,
F. Billings,
A. D. Blackader,
G. Blumer,
J. W. Brannan,
N. Bridge,
R. C. Cabot,
S. S. Cohen,
W. T. Councilman,
A. C. Cushny,
E. G. Cutler,
C. L. Dana,
F. Delafield,
G. Dock,
J. S. Ely,
H. C. Ernst,
J. Ewing,
R. H. Fitz,
S. Flexner,
F. Forchheimer,
M. H. Fussell,
C. L. Greene,
J. P. C. Griffith,
H. A. Hare,
L. R. Hektoen,
F. P. Henry,
J. B. Herrick,
C. A. Herter,
L. E. Holt,
Wm. F. Howard,
H. Hun,
A. Jacobi,
W. B. James,
E. G. Janeway,
E. P. Joslin,
A. O. J. Kelly,
F. P. Kinnicutt,
G. M. Kober,
H. Koplik,
H. A. Lafleur,
M. J. Lewis,
S. Loving,
A. McPhedran,
W. G. MacCallum,
F. B. Mallory,
A. V. Meigs,
S. J. Meltzer,
J. K. Mitchell,
S. W. Mitchell,
J. L. Morse,
J. H. Musser,
W. P. Northrup,
E. L. Opie,
Wm. Osler,
F. H. Williams.
W. H. Park,
G. L. Peabody,
F. Pfaff,
T. M. Prudden,
J. J. Putnam,
B. K. Rachford,
B. Robinson,
T. M. Rotch,
B. Sachs,
G. G. Sears,
H. Sewell,
G. B. Shattuck,
F. C. Shattuck,
A. A. Smith,
T. Smith,
M. A. Starr,
A. Stengel,
G. M. Sternberg,
D. D. Stewart,
J. Stewart,
C. G. Stockton,
W. G. Thompson,
E. L. Trudeau,
J. Tyson,
V. C. Vaughan,
H. Vickery,
A. S. Warthin,
Wm. H. Welch,
G. Wilkins,

Tuesday, May 12th.—Morning Session.

The Association was called to order at 10.05 A.M. by President Stewart, who then read the President's Address.

The Secretary read the list of nominees recommended by the Council for election to membership.

On the recommendation of the Council it was resolved that the amendment to the Constitution increasing the active membership be laid upon the table for action at the next annual meeting.

The Treasurer's report for the past year was read and referred to an Auditing Committee, consisting of Drs. Kinnicutt and Dock.

Dr. Janeway read a paper entitled "Bathycardia," which was discussed by Drs. Osler, Williams, and McPhedran.

Dr. Delafield read a paper entitled "Post-typhoid Sepsis," which was discussed by Drs. Koplik, Peabody, and Robinson.

Dr. Trudeau read a paper entitled "Artificial Immunity in Experimental Tuberculosis," which was not discussed.

Dr. T. Smith read a paper entitled "Studies in Mammalian Tuberculosis III. Description of a Bovine Bacillus from Man. Culture Test for Distinguishing the Bovine from the Human Type of Bacilli," which was discussed by Drs. Osler and Smith.

Dr. Kober read a paper entitled "The Transmission of Bovine Tuberculosis by Milk," which was discussed by Drs. Trudeau and Smith.

Dr. Koplik read a paper entitled "Primary Tuberculosis of the Tonsil; the Tonsil as a Portal of Tubercular Infection," which was not discussed.

Dr. Northrup read a paper entitled "A Skin Lesion Associated with Rapid Growth of Long Bones (Les Vergetures de Croissance, Jules Comby)," which was discussed by Drs. Jacobi, Osler, and Janeway.

Dr. Forchheimer read a paper entitled "Dermatomyositis," which was not discussed.

Drs. Holt and Park read a paper entitled "Observations upon Results Obtained in Infant Feeding with Various Forms of Milk in Tenements and Institutions in New York City," which was not discussed.

Adjourned at 1.10 P.M.

Wednesday, May 13th.—Morning Session.

The Association was called to order at 9.20 A.M. by President Stewart.

Drs. Thos. B. Futcher, of Baltimore; Charles F. Martin, of Montreal, and Robert B. Preble, of Chicago, were elected active members of the Association.

The Auditing Committee reported that they had examined the Treasurer's accounts and vouchers, and found them correct.

Dr. Kelly read a paper entitled "Acute Lymphatic Leukemia."

Dr. Kinnicutt reported an autopsy and microscopic findings in a case of acute lymphatic leukemia.

Drs. Dock and Warthin read a paper entitled "A Clinical and Pathological Study of Two Cases of Splenic Leukemia Presenting Early and Late Stages of Cirrhosis; Early and Late Stages of Banti's Disease."

These three papers were discussed by Drs. Cabot, Peabody, Herrick, Fussell, Welch, Osler, Kelly, Kinnicutt, Dock, and Warthin.

Dr. Morse read a paper entitled "The Relation of Chronic Enlargement of the Spleen to Anemia in Infancy," which was discussed by Dr. Osler.

Dr. Osler read a paper entitled "Chronic Cyanosis and Enlarged Spleen, with Polycythemia: A New Clinical Entity," which was discussed by Drs. Cabot, F. C. Shattuck, Stockton, McPhedran, Hare, Bridge, Stengel, Edson (by invitation), Joslin, and Cohen.

The Association adjourned at 11.55 A.M., to meet with the Association of American Pathologists and Bacteriologists, to listen to Dr. Councilman's paper on "The Micro-organism of Cancer."

Thursday, May 14th.—Morning Session.

The Association was called to order at 9.20 A.M., by President Stewart. The nominations of officers recommended by the Councillors were read.

Dr. Northrup read a paper entitled "Gonococcal Peritonitis in Children, Simulating Appendicitis," which was discussed by Drs. Kinnicutt and Jacobi.

Dr. Hare read a paper entitled "A Preliminary Report on the Influence of Alcohol in Infectious Diseases."

Dr. Cabot read a paper entitled "Studies on the Action of Alcohol upon the Circulation in Fevers."

These two papers were discussed by Drs. Welch, Jacobi, Abbott, Shattuck, Musser, Dock, and Cabot.

Dr. Rotch read a paper entitled "Infantile Scorbutus," which was discussed by Dr. Jacobi.

Dr. Griffith read a paper entitled "Sudden Death and Unexpected Death in Infancy and Childhood, with Special Reference to the So-called Thymus Death," which was discussed by Drs. Blumer and Jacobi.

Dr. Barker read a paper entitled "The Morbid Changes in Hereditary Ataxia," which was discussed by Dr. Starr.

Dr. Flexner read a paper entitled "Autolysis in Lobar Pneumonia," which was discussed by Drs. Jacobi, Meltzer, and Flexner.

Dr. Abbott read a paper entitled "The Adrenal Gland and Its Active Principles in their Relations to Cytolysis and Antitoxin Production," which was not discussed.

Dr. Pearce read a paper entitled "An Experimental Study of the Nephrotoxins," which was discussed by Drs. Cabot, Flexner, Sewell, MacCallum, and Pearce.

Dr. Meltzer, for Dr. Haven Emerson, read a paper entitled "Studies upon the Capsule of the Kidney," which was not discussed.

Dr Tyson, for himself and Dr. Frazier, read a paper entitled "Report of a Successful Decapsulation of the Kidney," which was discussed by Drs. McPhedran and Cutler.

Dr. Thompson read a paper entitled "Paroxysmal Hematinuria," which was not discussed.

Adjourned at 12.50 P.M.

Afternoon Session.

The Association was called to order by President Stewart at 2.45 P.M.

Dr. MacCallum read a paper entitled "Observations on Some Points in the Pathology of Thyroid and Parathyroid."

Dr. Joslin read a paper entitled "The Influence of Different Varieties of Fat on the Formation and Excretion of Acetone."

Dr. Henry read a paper entitled "Pulsating Serous Pleurisy."

Dr. McKenzie read a paper entitled "A Case of Extensive Pulmonary Infarction."

Dr. Tyson read a paper entitled "The Third and Final Report of a Case of Presystolic Mitral Murmur Complicating Pregnancy," with an exhibition of a specimen showing triple valvular lesion.

Dr. H. U. Williams read a paper entitled "Experimental Studies on the Eosinophilia of Trichinosis"—a preliminary communication.

None of these papers was discussed.

During the meeting the following papers were read by title:

"Clinical Observations on the Heart and Arteries of Individuals who Have Suffered from Typhoid Fever," by W. S. Thayer.

"Note on Typhoid Fever and Scarlatina," by L. Hektoen.

"The Visceral Lesions of the Erythema Group of Skin Diseases." Third series, by William Osler.

"Lymphatic Leukemia without Enlargement of the Lymph Glands," by George Blumer and H. C. Gordinier.

"Resemblance to Adrenalin of the Toxin causing High Tension Pulse in Nephritis," by Wm. H. Thomson.

"Actinomycosis of the Central Nervous System, with Report of a Case due to an Unidentified Member of the Actinomyces Group," by W. T. Howard, Jr.

"Infectious Forms of Myelitis," by B. Sachs.

"Cardiorespiratory Murmurs as Marks of a Certain Type of Neurasthenia," by James J. Putnam.

"Acute Bulbar Paralysis, with Clinical Reports and Autopsies," by Charles L. Dana.

"The Treatment of Migraine," by B. K. Rachford.

"A Further Report on the Study of Bacterial Cells," by V. C. Vaughan.

"Gastric Syphilis," by H. A. Lafleur.

"A Case of Extreme Malformation of the Heart," by J. H. Wright and A. K. Drake.

"Some of the Therapeutic Uses of the X-rays," by F. Williams.

"Intussusception, with Report of a Case of Recovery after Extrusion of Eleven Inches of the Ileum," by Norman Bridge.

"A Case of Disseminated Hemorrhagic Encephalomyelitis," by J. H. Wright.

"Typhoid Fever, an Analysis of Seven Hundred Cases," by J. McCrae.

"A Rapid Method of Hardening and Embedding Tissues," by B. M. Bolton.

The following officers were then elected by ballot:

President—Wm. T. Councilman.
Vice-President—Edward L. Trudeau.
Secretary—Henry Hun.
Recorder—Solomon Solis Cohen.
Treasurer—J. P. Crozer Griffith.
Councillors—Victor C. Vaughan, George M. Kober.

It was resolved that the thanks of the Asscciation be given to Mr. F. P. Hight, manager of the New Willard Hotel, for his courtesy in furnishing a room for this meeting.

It was resolved that the thanks and congratulations of the Association be tendered to President Stewart for the very successful meeting over which he has presided.

Adjourned at 4.30 P.M.

HENRY HUN,
Secretary.

ADDRESS OF THE PRESIDENT.

By JAMES STEWART, M.D.,
OF MONTREAL, CANADA.

In occupying the high position of President of the Association of American Physicians my first duty is to acknowledge the great honor conferred upon me.

Our Association is one whose work has made it known and respected wherever modern medicine is taught and practised. I can assure all the members that I appreciate very highly the compliment paid not only to myself but to my colleagues across the line. The generous manner in which Canadians have been received in this Association from the very beginning, eighteen years ago, is a matter for which we are all deeply grateful. We have felt from the first at home.

The existence of this Association of clinicians, pathologists, bacteriologists, and chemists is an index of the ever-advancing character and increasing precision of our work. In contrasting the work performed by the Association since its inception, in 1886, with that of the last two or three years, it will be at once apparent that there has been a considerable change in the character of the papers read. The proportion of more or less purely scientific papers has been steadily increasing in number and in value.

From the beginning of our work the papers of the more or less purely clinical type have been from the first of a high order, and they continue to be of the same high character.

Our programme for this meeting is an index of much valuable and laborious work that we shall have the pleasure of hearing during the session. In the words of a recent writer in the Edinburgh *Review:*

"The new century begins its history from a vastly higher standpoint all round than its predecessor did.

"Our chief hope for the future lies in the desire, which has become so much more acute and general within the last few years than,

perhaps, ever before, to get away from the bondage of theories and hypotheses and to be able to question and cross-question facts until their final meaning becomes plain. The true students of medicine are to-day everywhere struggling to get to the heart of the disturbing influences which break up the harmony of health and life. What is looked for and asked for now is not for petty nostrums against this ailment or the other, but for the wisdom which shall make them privy to the mystery of knowledge in all that concerns health."

It is most gratifying to find the prominent part many members of this Association are taking in the solving of the different problems that have so long resisted patient investigation.

The very recent splendid contribution to practical medicine made by one of our members will stand forever to the glory of American medicine.

The noble way in which hospitals and research laboratories have been endowed both in the United States and Canada is a matter that we should always take fitting opportunities to express our heartfelt gratitude for.

It is a harbinger of a time that will, we hope, come when the recurring waves of charlatanism shall cease. The names of Johns Hopkins, Rockefeller, Morgan, Vanderbilt, Strathcona, and many others will live to be blessed for ages.

Before closing my introductory remarks it is my duty to refer officially to our fellow-members who have been taken from us during the past year. We have lost three members since our last meeting, all men of high promise, all of whom have left behind them evidence of excellent and abiding work.

The death of Dr. Wyatt Johnston, which occurred on June 19th, deprives the Association of one of its most promising members. His death was due to septic poisoning acquired in the postmortem-room of the Montreal General Hospital. He was a graduate of McGill University in the year 1884. During his student days he showed great enthusiasm for pathologic work, and under Dr. Osler's direction soon laid a thorough foundation in pathology. After a year's work as a resident in the Montreal General Hospital he proceeded to Germany, first working under Virchow, and afterward with Grawitz at Greifswald. He subsequently spent a considerable time in working

in comparative pathology in Munich and in the Zoölogical Gardens in London. He was early attracted to the sanitary application of bacteriology, and also its application to the diagnosis of disease. His modification of the Widal reaction by means of dried serum is a simple and effective test. He was the first to announce the diagnosis of diphtheria by culture on hard-boiled eggs. He also introduced a simple method for the diagnosis of leprosy, as well as other modifications of various differential tests, all of which tended toward simplification.

In recent years he devoted himself to hygiene and medical jurisprudence, and the high character of his work in both departments had given him a reputation as an able and trustworthy investigator. His colleagues and friends feel that in his untimely death each has lost a bright and cheering companion and a friend whose earnestness of purpose and enthusiasm in his work was a stimulus to all who came into contact with him, "one who was a high type of intellectual honesty combined with singular simplicity and modesty regarding his own capacity and the importance of his valuable original work."

The death of Dr. Frederick A. Packard, on November 1st last, from typhoid fever, is a great loss to the Association. Although a young man, he had already reached a high position among the physicians of the country. He graduated at the University of Pennsylvania in 1882, and from the Medical School in 1885, where he had an unusually bright career. His subsequent opportunities as resident physician in the University Hospital, and afterward in the Pennsylvania Hospital, he made excellent use of. After his term of service in the latter had expired, he was successively appointed physician to the outdoor department of the Episcopal and the Pennsylvania Hospitals, and later physician to these hospitals and also to the Philadelphia and the Children's Hospitals.

During the illness of Professor H. C. Wood, in the session of 1901–1902, Dr. Packard conducted the course in Pharmacology and Therapeutics with great success. Besides writing a work on dietetics, he contributed a number of articles to Keating's *Encyclopædia of the Diseases of Children.* His appointment as a Trustee of the University of Pennsylvania was universally acknowledged as a happy one for the institution. In every relation of life Dr. Packard's sterling

qualities distinguished him as an unusual man. His loss to medicine and to his own community is most unfortunate.

The death of Dr. Walter Reed, which took place in Washington on November 23d, is another loss of a severe character that this Association and the whole profession keenly deplores. His death was caused by appendicitis. He graduated at the Medical Department of the University of Virginia in 1869, and in 1872 from the Bellevue Hospital Medical College. He entered the army as an Assistant Surgeon in June, 1875. In 1890 he was sent to study pathology and bacteriology under Dr. Welch at the Johns Hopkins University. It was here that he carried out a valuable research on the causes of hepatic complications in typhoid fever. After leaving Baltimore he became identified with the Army Medical Museum, in which he organized the pathologic and bacteriologic laboratories, which afterward became departments of the Army Medical School. His fame will, however, mainly rest on the remarkable series of researches that he conducted in conjunction with Drs. Carroll, Lazear, and Agramonte, the other members of the Yellow Fever Commission of the United States Army. The startling results of this great work have conferred a boon on humanity that will take rank with the discovery of vaccination, antitoxin for diphtheria, and the mosquito agency in the spread of malaria.

BATHYCARDIA.

By E. G. JANEWAY, M.D.,
OF NEW YORK CITY.

For the past twenty-five years I have been interested in the matter of low hearts. The incitement thereto was, in part, that at one time I was in possession of two hearts, one obtained from the dissecting-room and the other from an autopsy. Each of these was provided with an abnormally long ascending portion of the arch of the aorta. It had, in consequence, aroused in my mind the idea that this fact would, at least in part, explain the condition of low heart in people who otherwise seemed, and on examination were found, practically well; at least, they were not proved to have any disease of the heart or of the lungs. Hence it was a satisfaction when I found that at a meeting of the Society for Internal Medicine at Berlin, in October, 1900, Mosse introduced the word bathycardia to designate a heart which, in an otherwise healthy man, occupied a position lower than the ordinary one. It is particularly emphasized that the lungs and the heart were normal and the latter not specially mobile, and that the state persisted on a number of examinations. It has seemed to me that this word is a particularly good one. We now employ the words bradycardia and tachycardia, and I can see no objection to the addition of this newest one. My young friend William Prentice, Professor of Greek in Princeton University, considers it appropriate and more euphonious than another which could be employed. Professor Mendelsohn has written a very readable article on this condition in the *Festschrift* for Professor Von Leyden on the completion of his seventieth year, laying considerable stress upon the state of heart, upon the length of the vessels, and upon the possibility of the lowering of the heart without considering it entirely dependent upon the descent of the diaphragm. F. Sibson, who made most careful studies about the topography of the heart and great vessels, and also

of the measurement of these, as well as of their relationship to the chest, wrote about the length of the aortic arch and also of its permitting or being associated with a lower position of the heart. He does not, however, apparently consider that this could cause or permit of a marked lowering unless the diaphragm became depressed from other causes.

The recognition of the condition is not a matter of difficulty, though, undoubtedly, the assumption is that the heart is overlapped by the lungs or that these latter are emphysematous. I have assured myself in the cases which have come under my observation that the lowered position of the heart is responsible for the resonance which is encountered on percussion over that upper area where, ordinarily, dulness is obtained on deep percussion; then resonance on percussion, or, better expressed, absence of cardiac dulness in the usual situation of the base of the heart, is one of the signs. Again, the sounds of the heart, especially the second sounds of the heart, are not distinctly heard until we reach a position decidedly lower than the ordinary one.

The apex impulse of the heart is perceived also at a lower level, in the sixth space not infrequently, where it may be made out at times only with considerable difficulty. The result of the lowered position of the heart is to bring it into more close relationship with the stomach, and hence with flatulence or other disturbance of the organ there is greater liability to have uncomfortable sensations or palpitation; yet when we consider the number of people with normally placed hearts who have more or less discomfort brought about by gastric conditions, it raises the question whether we are not liable to assume too much because of the theory that it should be so. Mendelsohn, of Berlin, has, as above noted, laid stress upon this point.

Another point which has been of some interest is that the depression of the liver is not so marked as one would anticipate, in view of the descent of the diaphragm. In the five years past I have met six instances of the condition; one, however, should be excluded because of coexisting hypertrophy of the heart. The different factors which exist may hence lead to the assumption that the lung state is the main condition, or else that the heart is small, or that because the diaphragm is lower that this is the only essential factor; or, finally,

that because the left lobe of the liver is lower when the diaphragm is depressed, hence the whole condition can be explained in this way.

I have been pleased to find a word for this condition which does not seem to prejudge the condition, and, accordingly, I am prepared to follow Mosse's use of the word bathycardia rather than cardioptosis. I have brought with me a radiograph of one of the latest cases which have come before me, and think that it will illustrate, better than a long description, the heart in a lower position than normal. It is to be stated that examination with the fluoroscope gave a very satisfactory result. In no case which I have watched have I thus far obtained a postmortem examination in order to make such study of conditions as should satisfy me about the points here raised; still it is to be remembered that unless an autopsy were made by some one familiar with antemortem conditions little might be learned, as the rigor mortis and the usual forced expiration would not allow maintenance of conditions which had obtained during life.

DISCUSSION.

DR. OSLER: A very interesting condition is the descent of the heart in great hypertrophy, particularly that of the right heart, when there may be a distinct bulging in the left parasternal line below the costal margin. I have known it to be mistaken for aneurism. The cases that I have seen were mitral stenosis with great hypertrophy of the right heart.

DR. F. H. WILLIAMS: I should like to ask the writer if there was any record made of the position of the tube and its distance from the patient when the radiograph was taken? The accuracy with which the radiograph presents the position of the heart, for instance, depends upon these two points, and a knowledge of them is necessary in order to interpret the conditions accurately; therefore, it seems to me important that the position and distance of the tube should be indicated in some way on the radiograph. For some years I have been in the habit, when taking a radiograph of the chest of a patient, for instance, of placing a metal washer over the median line of the sternum at the point where it crosses the line marking the lower border of the fourth rib, and of putting the anode of the tube exactly opposite the washer and at a fixed distance of 70 centimeters (28 inches). The shadow of the washer in the radiograph serves as a memorandum of the point opposite which the tube was placed, and by means of it and a knowledge of the distance of the tube, which can be noted on the radiograph, the practitioner is

better able to appreciate the differences in the size and position of the heart, for example, than would otherwise be possible. If a system were adopted of placing the tube opposite a given point and at a fixed distance from the patient, radiographs of cases taken by physicians in different parts of the world could be compared. I hope such a system will soon be adopted; its advantages are so evident that they need not be dwelt upon.

Dr. McPhedran: In regard to the point made by Professor Osler, of great hypertrophy of the right ventricle, I should like to know if he refers to the hypertrophy and dilatation? A few days ago we had a death from mitral stenosis, without dilatation of the right ventricle, but with extreme hypertrophy. The man died of hemorrhage due to rupture of markedly atheromatous vessels. He had a large, well-developed chest and no sign on the thorax of any derangement at all.

Dr. Janeway: Dr. Caldwell took these photographs, and I do not know the exact distance of the tube from the patient. It was done rather to show the position of the heart than anything else.

THE TRANSMISSION OF BOVINE TUBERCULOSIS BY MILK, WITH A TABULATION OF EIGHTY-SIX CASES.

BY GEORGE M. KOBER, M.D.,
OF WASHINGTON, D. C.

THE agency of milk in the causation of scrofula was referred to by Carmichael,[1] in his essay on the nature of scrofula, with evidence of its origin from disorders of the digestive organs, London, 1810, in which he refers to *acescent* diet, especially of cow's milk, as a frequent cause. On page 50 he says: "Infants at the time of weaning are from the change of diet particularly subject to bowel complaints, too often followed by disease of the mesenteric and lymphatic glands."

He quotes Richard Wiseman (1626–1686), White (1787), and Lieutand to show that whenever the outward glands do appear swollen, you may safely conclude the mesenteric to be so, too, they being usually the first part that is attacked by this malady. Indeed, Carmichael, while he never saw a subject in the dissecting-room with strumous glands externally without a similar state of those of the mesentery, claims that he has very frequently seen the latter unaccompanied by any affection of the external glands, which to his mind indicates that in scrofula the mesenteric glands are the first involved.

While Carmichael did not attempt to prove the transmission of scrofula in the milk of diseased cows, he points with emphasis to the use of sour milk, and on page 101, remarks:

"With respect to the disease in question, we know that swine are so subject to one very similar, that scrofula has in consequence derived its name from those animals, and certainly their extraordinary fondness for *acescent* food corroborates in some degree the foregoing opinion. Swine, it is well known, fatten upon buttermilk and upon the sour liquid formed in starch manufacture during the steeping of wheat."

These are suggestive statements, especially as, in the opinion of veterinarians of the present day, tuberculosis is increasing among swine, largely as a result of consuming tuberculous milk. According to Salmon,[2] during the year 1900 of 23,336,884 hogs slaughtered under Federal inspection, 5444 were sufficiently affected to cause condemnation of some part of the carcass.

Casper,[3] in his *Characteristics of French Medicine*, etc., published in 1822, on page 124, writes:

"Scrofula is not more rare in Paris than elsewhere, and baffles also here the efforts of physicians. La Billardière declares that the majority of milch cows in Paris perish from nodular consumption, and that their milk contains seven times more of lime phosphate than common. It is possible that there is a connection between this phenomenon and the many tuberculous diseases among the children in Paris. We cannot pursue here this investigation, where the mere fact suffices that in Paris, especially in the hospitals for foundlings and for children, like the St. Louis and others, the sequela and effects of scrofula can be seen in astonishing numbers."

La Billardière's[4] statement that the milk of tuberculous cows contains seven times more of lime phosphate than common is of special interest in view of Dr. de Schweinitz's[5] recent biochemical researches upon bovine, swine, avian, virulent human and attenuated human tubercle bacilli, in which he calls attention to the large amount of phosphoric acid obtained from the germs, and also points out that the conclusions which might be drawn from these analyses indicate a closer resemblance in the composition of the germs between the moderately virulent human and the very attenuated human bacilli.

Klencke,[6] in 1846, was the first to write on the infectiousness and transmission of scrofula by cow's milk. In his book of ninety pages he gives the clinical histories of sixteen children who had been fed with the milk of scrofulous and tuberculous cows, and they all point to tuberculosis of either the intestines, glands, skin, or bone. He also describes the condition of the seven suspected cows, and verified the diagnosis of a "scrofulous-tuberculous condition" in four postmortem examinations of the cows, which demonstrated to his satisfaction "that the same scrofulous lesions may be developed in the cow as are found in the human subject and that human scrofula and the disease found in the mammalia are identical." The details of these cases were republished by the writer in 1895.

Klencke's contribution to the early literature of this subject may be regarded of special value, as he was one of the first to demonstrate the infectious nature of tuberculosis by injecting, in 1843,[7] human tuberculous matter into the cervical veins of rabbits, causing pulmonary and hepatic tuberculosis in these animals. In passing it should be stated that inoculation experiments had been made by Kortum (1789), Hébréad (1802), Salmade (1805), Goodlad and Deygallières (1829), Lepelletier (1830), and Laennec and Erdt (1834[8]). These experiments naturally paved the way for Villemin's[9] brilliant and positive demonstrations in 1865.

Since that time numerous instances of artificial tuberculosis have been reported; the experiments having been performed on heifers, calves, goats, swine, guinea-pigs, rabbits and dogs. So, for instance, under the heading of *subcutaneous inoculation methods* may be mentioned the work of Soujou and Court Paul,[10] Gerlach,[11] Günther and Harms,[12] Rivolto and Perroncito,[13] Bagge,[14] Zürn,[15] Bollinger,[16] Biffi and Verga,[17] Bouley,[18] Aufrecht,[19] Toussaint and others. *Intraperitoneal inoculations* were reported by Klebs,[21] 1870, Bollinger,[16] 1873, and Kitt,[22] 1878. *Intravascular inoculations* were reported by Semmer, Thal, and Nesterow.[23] *Intraocular inoculations* were reported by Cohnheim and Salomonson,[24] Hänsell and Deutschmann,[25] and Baumgarten;[26] and finally the *inhalation experiments* by Tappeiner,[27] Lippl, Reinstadler and Bertheau[28] may be cited.

It is true that opposing views were held and quite a number of negative experiments have been reported, but on the whole the results were sufficiently numerous and uniform to demonstrate the identity of scrofula and tuberculosis and the intercommunicability of tuberculosis in animals and man. This evidence was materially strengthened by the feeding experiments of Gerlach,[29] Chaveau,[30] Bollinger,[31] Klebs,[21] Zürn,[15] Roloff,[32] Brell,[33] Metzguer,[34] Langeron,[35] Blumenberg,[36] Orth,[37] Lange,[38] Peuch,[39] Peuch and Toussaint,[40] Aufrecht,[41] and others.

Bollinger[42] in the discussion of artificial tuberculosis before the German Naturalists and Physicians in 1879 (which was participated in by v. Recklinghausen, Arnold, Birch-Hirschfeld and Fränkel), had no hesitation in declaring that milk from tuberculous cows is largely responsible for the production of scrofula, which affects about 70 per cent. of the children in Munich.

E. Klebs,[43] from his experiments in 1871–1873, concluded that milk from tuberculous cows produces tuberculosis in different animals, that the disease commonly begins with an intestinal catarrh, followed by tuberculous affections of the mesenteric glands, involvement of the liver and spleen, and finally by extensive miliary tuberculosis of the pulmonary organs, and Virchow,[44] in 1880, suggested that bovine tuberculosis may be conveyed in the milk, especially if the udder be the seat of the lesion. In the meantime a number of cases of transmission of bovine tuberculosis in milk had been reported by Schoengen,[45] Leonhardt,[46] Bollinger and Stang,[47] Demme,[48] Epstein,[49] Uffelmann,[50] Johne,[8] and Law.[51] Creighton,[52] in 1881, published a book on bovine tuberculosis in which he presents a minute study of a number of cases of tuberculosis in man which had the characteristics of an infection and at the same time a suggestive likeness in the morbid products to the bovine form of tuberculosis (*Perlsucht*). Indeed, the evidence on this subject appeared sufficiently strong to justify Koch[53] in 1882 in declaring:

"It is not the peculiar structure of the tubercle, nor its lack of blood-vessels, nor the presence of giant cells, that will give the solution, but rather the proof of the tuberculosis bacillus, whether it be in the tissue by means of staining reaction or whether it be by means of culture upon coagulated blood serum. This criterion being adopted as a foundation principle, according to my investigations miliary tuberculosis, caseous pneumonia, caseous bronchitis, intestinal and glandular tuberculosis, bovine tuberculosis, spontaneous and inoculation tuberculosis of animals must be declared as identical. . . . Bovine tuberculosis is identical with human tuberculosis, and, therefore, a disease transmissible to man. It should be treated just like other infectious diseases transmissible from animals to human beings. However great or small may be the danger which results from the consumption of meat or milk affected with bovine tuberculosis, it is present, and must be, therefore, avoided.

Soon after Koch's discovery of the tubercle bacillus diligent search was made for the presence of this organism in the milk of diseased cows, and it was demonstrated by Csokor,[54] Bang,[55] Johne,[56] Bollinger,[57] May,[58] Ernst,[59] Woodhead and MacFadyean,[60] Martin,[61] Nocard,[62] Stein,[63] Hirschberger,[64] and others. Some observers, notably Martin[61] and Nocard,[62] found that milk was infective only when the udder was itself the seat of tuberculous lesions, but Ernst, as early as 1889, and Theobald Smith,[65] in 1893, from a number of experimental observations, concluded that tubercle bacilli may be present in the milk of

tuberculous cows when the udder, so far as the naked eye could tell, contained no focus of disease. These conclusions are, moreover, supported by the investigations of Bang, Stein, Bollinger, Adami, Delépine and Hirschberger.

Quite a number of observers failed to find tubercle bacilli in the milk of tuberculous animals, but May[58] and Hirschberger[64] proved that the inoculation experiments are the more certain guide as to whether the milk is infectious or not, since they obtained positive results from milk of undoubtedly tuberculous animals in which they were unable to demonstrate the presence of tubercle bacilli. As a matter of fact, Rabinowitsch and Kempner[66] obtained positive results in inoculation experiments with the milk of ten out of fifteen cows that had reacted to tuberculin, and only two of these animals revealed udder lesions.

The general results of inoculation experiments differ in different countries, and naturally vary with the prevalence of bovine tuberculosis, the mode of technic and many other factors.

The reports indicate that the infectious qualities are greatest with milk from animals with udder lesions, and next from those affected with general tuberculosis.

Bollinger[67] found that the general market milk of Munich proved infectious in 16.6 per cent. of the animals; Martin in Paris, in 33 per cent; Bang in Copenhagen, in 15.5 per cent.; Ernst in Boston, in 12 per cent.; Fiorentini in Milan, in 10 per cent.; Rabinowitsch, in 28 per cent.; Obermüller, in 7.5 per cent.; Paris Municipal Laboratory, in 40 per cent; Hamilton, Boyce, Woodhead, and Delépine in Liverpool, in 29 per cent.; Delépine in Manchester, in 25 per cent.; Massone, in 9 per cent.; Ott, in 11.6 per cent.; Jäger in Königsberg, in 7 per cent.; Kanthack and Sladen[68] found more than 50 per cent. of the milk supplied to the college in Cambridge infectious.

The experiments reported by Schmidt-Mühlheim, May, Stein, Hirschberger and Bang, and which were made with milk from tuberculous cows, proved successful in 60 to 70 per cent. of the animals.

In addition and, perhaps, of greater importance to the subject are, of course, the feeding experiments. Disregarding the earlier experiments of Gerlach and Bollinger, we have the important and positive results obtained by Baumgarten,[70] Wesener,[71] Fischer,[72] Peuch,[73] Ernst,[74] Bang,[55] Falk,[75] Zagari,[76] and Gebhardt,[77] showing that after a variable period, usually between eleven and twelve weeks, the ingestion

of tuberculous milk developed a classical tuberculosis either of the intestinal mucosa and mesenteric glands, or spleen and liver, followed by subsequent involvement of other organs. In some, but not many, of these cases there was evidence of primary intestinal tuberculosis, but almost all of the cases revealed infection of the mesenteric glands. In the cases where the primary lesions were found elsewhere than in the intestines or mesenteric glands, Wesener,[71] in 1885, suggested that the bacilli must have found their way into the general circulation. As a matter of fact, the experiments of Dobroklonski,[78] Desoubry and Porcher,[79] of Nicolas and Descos,[80] have since shown that microbes may pass through the intestinal wall and enter the thoracic duct. The last-named experimenters, in 1902, brought out the interesting fact that three hours after the ingestion of tubercle bacilli the chyle and the lymph of the thoracic duct may contain bacilli in sufficient number to infect a guinea-pig, and we know from Wyssokowitschky's[81] experiments that from eight to thirty virulent tubercle bacilli introduced into the peritoneal cavity of a guinea-pig are required to bring about infection.

It should be stated that in the feeding experiments by Günther and Harms,[82] Siedamgrotzky,[83] Roloff,[32] Bollinger,[42] and Nosotti, the results were not uniformly successful, and that Schreiber,[85] Günther and Harms[82] have reported negative results.

On the whole, however, the feeding experiments with tuberculous milk proved infectious in about 45 to 50 per cent. of the cases. This seems excessive, probably because many of the negative results were never reported.

Apart from these experiments, we have the reports of Lucas and Morro,[86] Utz,[87] Klebs,[88] Kruckow,[89] Pfennigwerth,[90] Vollers,[91] Woodhead,[92] and others to show that the disease may be transmitted in milk to calves and pigs and other animals.

It is interesting to note that Bang,[55] May,[58] and Woodhead,[60] noted a marked difference in the resulting lesions with raw milk and milk which had been subjected to different degrees of temperature. So, for example, Bang found that while a temperature of 158° F. did not destroy the vitality of the organisms it reduced their virulence, and Woodhead, by the operation of certain low temperatures, obtained a diminution in the virulence of the tuberculous material in milk, which then "became so tardy in its operation on the test animals as

to simulate the slower forms of consumption seen in the human subject, or when used to feed pigs, animals having some specialties of throat structure like that of man, gave rise to chronic enlargement of the throat glands, resembling the scrofulous glands so common in children."

In the meantime 56 additional cases of transmission of bovine tuberculosis through the medium of the milk supply had been reported by Law,[93] Demme,[94] Sonntag,[69] Meyerhoff,[95] Hermsdorff,[96] Northrup,[97] Ollivier,[98] Wyss,[99] Gosse,[100] Rotch and de Schweinitz,[102] Law,[103] Rich,[104] J. L. Smith,[105] Ernst,[74] Brouardell,[106] Von Ruck[107] Hills,[108] Prümers,[109] and Bovaird.[109] A number of accidental inoculations (wound infections) in man with bovine bacilli had also been placed on record by Pfeiffer,[110] Hartzell,[111] Rich,[104] Tscherning,[112] Law,[113] Ravenel,[114] Naughton[115]. These and the cases reported by Grothan,[116] Coppez,[117] Priester,[118] of primary subcutaneous tuberculosis caused by the topical application of cream, infection in milking, and the introduction of infected milk in the attempt to remove tattoo marks, had materially strengthened the evidence as to the transmissibility of bovine tuberculosis to man. Indeed, the absolute identity of tubercle bacilli infecting mammalia was generally assumed until Theobald Smith,[119] in 1896, presented to the Association of American Physicians a comparative study of a bovine bacillus and a presumably human bacillus in which the morphologic and biologic differences were sufficiently marked to suggest further study, and as a result of this research Smith,[120] in 1898, stated that "We are justified if only to guide and stimulate further study in establishing a distinctively human or sputum and a bovine variety of the tubercle bacillus." He also expressed the opinion that the comparative study of the tubercle bacilli will lead to some definite understanding on certain important questions and eventually to more light on the whole subject of tuberculosis from the preventive as well as the therapeutic side. Notwithstanding these facts and the observations of Martin,[61] in 1895, that human sputum was far less virulent for animals than was bovine tuberculous material, the announcement of Koch before the International Congress for the prevention of tuberculosis, held in London July 22 to 26, 1901, was received with astonishment, especially since his conclusions carry with it a reversal of his judgment rendered in 1882.

Koch in his address of 1901, makes the following declarations:[121]

"1. The bacilli found in cases of bovine tuberculosis are much more virulent for cattle and other domestic quadrupeds than the bacilli found in cases of human tuberculosis.

"2. This difference is so marked and so constant that it may be relied upon as a means of distinguishing the bacilli of bovine tuberculosis from those of the human disease, even assuming that the former may occasionally be found as a cause of disease in man.

"3. If bovine bacilli are capable of causing disease in man, there are abundant opportunities for the transference of the bacilli from the one species to the other, and cases of primary intestinal tuberculosis from the consumption of tuberculous milk ought to be of common occurrence. But post-mortem examination of human beings proves that cases of primary intestinal tuberculosis are extremely rare in man, and, therefore, it must be concluded that the human subject is immune against infection with the bovine bacilli, or is so slightly susceptible that it is not necessary to take any steps to counteract the risk of infection in this way."

Fortunately for the advancement of science, opposition fosters the spirit of inquiry, and many experiments have been made which have shed new light upon the already voluminous testimony. While it is true that the results in the feeding experiments with human sputum have varied, and that some of the earlier experimenters have reported negative results, the weight of the testimony is clearly in favor of the intercommunicability of human and bovine tuberculosis, and the experiments made during the past two years by Ravenel,[122] de Schweinitz,[123] Mohler,[123] Orth,[124] de Jong,[125] Stenström,[125] Fibiger,[125] Wolff,[125] Nocard,[125] Arloing,[125] v. Behring,[125] Dean and Todd,[125] and Cipollina[135] conclusively demonstrate that cattle are not refractory to human tuberculosis and that bovine tuberculosis may be transmitted to monkeys. Whatever differences have been observed may very properly be attributed to the condition of the host, and to the different degrees of virulence found in human bacilli, as shown by the work of Vagedes,[126] 1896, Lartigan,[127] and Delépine.[128]

The former studied twenty-eight human cultures, and found one much more virulent than the others, and even more virulent than either of the two bovine cultures. Lartigan found bacilli of different degrees of virulence in human tuberculosis, and one of his specimens presented morphologic and cultural peculiarities which suggested the bovine origin described by Smith. Delépine obtained from the human

subject bacilli just as virulent as the bovine organisms, although in most instances the human tubercle bacillus was less virulent.

The writer has tabulated 86 cases of milk bovine tuberculosis, and quite a large number of cases of transmission of bovine tuberculosis to man have been reported by Krause,[128] Ravenel,[129] Lassar,[125] Huls,[125] Spronck and Hoefnagel,[125] and Troje.[137] New light has also been shed upon the extent of intestinal infection by the statistics of Heller,[130] who finds that in 714 autopsies in children who died from diphtheria 140 (19.6 per cent.) were tuberculous, and of these 30.7 per cent. showed primary lesions in the intestines or mesenteric glands; 2 (1.43 per cent.) showed primary intestinal tuberculosis; 8 (5.7 per cent.) showed primary intestinal mesenteric glands; and 33 (23.5 per cent.) showed primary mesenteric gland tuberculosis.

Bovaird's[131] collection of primary intestinal tuberculosis in children is summarized as follows:

	Total.	*Intestinal.*	*Per cent.*
German	236	9	4
French	128	0	0
English	748	136	18
American	369	5	1

Dr. Bovaird confesses his inability to understand or explain the difference. The facts are that the postmortem returns are extremely conflicting, and, unless accounted for by a variable prevalence of bovine tuberculosis and the habit of feeding raw or sterilized milk, suggest the necessity of more careful postmortem work.

The statistical work by Gottstein[132] shows that the mortality from tuberculosis in breast-fed children is but slightly more than half as much as among those otherwise nourished, the proportion being as 6 : 10. Salmon[133] has analyzed the vital statistics of Massachusetts and finds an increase of 36 per cent. in the forms of tuberculosis other than phthisis in the class under five years of age, while there was a reduction in the mortality of phthisis at all other ages of about 45 per cent., and the vital statistics of Michigan from 1885 to 1900 show also a tremendous increase during the milk-drinking age.

Dr. Hand's[136] statistics are as follows:

	Cases.	*Per cent.*
Total number of autopsies	332	
Total number showing tuberculosis	115	34.6
Apparent portal of infection (Hutinel's tuberculous chancre).		
Oldest lesion in the bronchial glands	75	62.2
Oldest lesion in the mesenteric glands	10	8.7
Process so general that the portal could not be determined	27	23.4

The cases of milk-borne tuberculosis, now numbering 86, while not as large as commonly supposed, are considerable when we consider the difficulty of tracing the infection on account of the more insidious character of the disease. In this connection we should remember that the first milk-typhoid epidemic was reported by Jacobs in 1858; in 1881 Mr. Ernst Hart had collected fifty epidemics, and in 1900 the writer tabulated 195 such epidemics. The opportunities for tracing bovine infection are much better in small communities and in isolated farm-houses than in large cities, and we should look to the country practitioner for help; he, in turn, unless properly equipped to verify his diagnosis, should apply to the Bureau of Animal Industry, or to the pathologist and bacteriologist of his medical school to check up his work.

A careful review of the cases recorded, when taken in connection with the laboratory experiments and the general evidence, justify the following conclusions:

1. Tuberculosis may be transmitted to man in milk from tuberculous cows; the danger from this source is real, and cannot be measured by the actual number of recorded cases, but should be judged in part, at least, by the inoculation and feeding experiments and the accidental wound infections which have established the intercommunicability of bovine and human tuberculosis.

2. The degree of danger may also be estimated by the prevalence of bovine tuberculosis and of the forms other than phthisis pulmonalis in man, remembering that the infectious qualities of milk are greatest when the udder is the seat of lesions, and that Gebhardt's experiments have shown that tuberculous milk when diluted with the milk of sound animals in the proportion of 1 : 40 lost its infective power.

3. The experimental studies also indicate that while the bacilli of human tuberculosis possess different degrees of pathogenic power and are often of feeble virulence for cattle, Koch's assumption that human and bovine tuberculosis are distinct and that human tuberculosis cannot be conveyed to cattle appears to be disproved, and his failure to secure similar results may be attributed to the use of human bacilli of diminished virulence.

4. Recent investigations have strengthened Smith's claim that there are two types of tubercle bacilli: the so-called bovine and human types, possessing certain morphologic and biologic differences; but it

has also been shown that virulent cultures may be obtained from both of these types, which, when inoculated into animals, produce the disease in question.

5. Further research seems desirable with a view of determining the frequency of primary intestinal and abdominal tuberculosis in all cases which come to autopsy, whether the child perished from tuberculosis or not, and in these autopsies the bacteriologic examination should be directed to the existence of the two types of tubercle bacilli originally referred to by Smith, and whether the bovine type predominates in the so-called scrofulous lesions.

6. Careful chemical analyses of the milk of tuberculous animals should be made with a view of determining the amount of phosphoric acid as compared with the quantity in normal milk, since it appears probable from Dr. de Schweinitz's biochemical researches that the excess noted by the older chemists is really the result of bacterial activity in the udder of the cow.

7. In the meantime the pathologist has no occasion to reverse his opinion as to the identity of human and bovine tuberculosis, and the sanitarian has no reason to assume that the human subject is immune against infection with the bovine bacilli or is so slightly susceptible as to cause him to relax his efforts in preventive measures.

The writer desires to express his acknowledgments to Dr. D. E. Salmon, Chief of the Bureau of Animal Industry, U. S. Department of Agriculture, for material assistance in the preparation of this paper, by placing at his disposal unpublished reports of experimental work.

Abstracts of Reports of Cases of Tuberculosis Attributed to Infected Cow's Milk.

Cases 1 to 16, 1846. Professor Klencke,[6] in a book of ninety pages, gives the clinical histories of sixteen children who had been fed with the milk of "scrofulous-tuberculous cows," and all of these cases point to tuberculosis of either the intestines, glands, skin, or bone. In three of the intestinal disorders he refers to the presence of indurated mesenteric glands. Of these cases one died, and two at the time of the report were in a hopeless condition. The clinical histories show that four of the children had been fed with milk from Cow B, three received their supply from Cow D, four from Cow E, two from Cow F, and three from Cow G. Professor Klencke, having connected these cases with a particular milk supply, extended his investigation into the condition of the cows—their sanitary environments—together with a chemical and microscopic examination of the milk, and actually followed up his inquiry by four autopsies of the cows, in which he demonstrated scrofulous-

tuberculous lesions. Such a course is worthy of emulation, and almost complies with the conditions of proof exacted by Professor Koch. Copious abstracts of these cases were published by the writer in the report of the Health Officer, District of Columbia, 1895.

Case 17. Schoengen,[45] at a meeting of the Veterinary Society held at Cologne, October 18, 1873, related the history of a child who, upon the advice of the family physician, was placed on cow's milk and developed undefined symptoms suggestive of tuberculous infection. An examination by a veterinarian of the cow resulted in a diagnosis of perlsucht, which was confirmed by postmortem. A change of the milk resulted in subsequent improvement of the child.

Cases 18 and 19. K. Leonhardt,[46] December, 1874, reports the case of a child, previously healthy, which contracted tuberculosis soon after being weaned, and died. The autopsy revealed tuberculous meningitis and extensive lesions of the intestines and mesentric glands, which were undergoing caseous degeneration; attributed to the use of unboiled milk from a tuberculous cow.

The second case, also one of tuberculous meningitis, occurred in a previously healthy child after the consumption of milk from a cow which, upon examination, proved to be tuberculous.

He also mentions the history of a forester's family in which the children, although previously perfectly healthy, invariably developed tuberculosis after weaning. The cow was finally slaughtered, and the autopsy revealed extensive tuberculosis. A child, born subsequently, remained perfectly healthy.

Case 20. Professor O. Bollinger,[47] January 25, 1876, reports that Dr. Stang, of Amorbach, treated a boy five years of age, well developed and of healthy parentage; no family history of tuberculosis for two generations. The child first developed symptoms of tabes mesenterica, and died some weeks later of miliary tuberculosis of the lungs, with enormous hypertrophy of the mesenteric glands, which were also undergoing caseous degeneration. While the postmortem was being made it was ascertained that a short time previously the parents had a cow slaughtered, which was found by the veterinary surgeon at the abattoir to have phthisis pommelière. This cow had been a good milker, and for a long time the boy had been in the habit of drinking its milk, directly after the milking, in a raw state.

Case 21. Professor R. Demme,[48] 1879, reports the case of a previously healthy boy who was breast-fed until the fifth month, after which he was fed on cow's milk, and developed intestinal tuberculosis involving the mesenteric glands. The child died after three months' illness. Postmortem examination revealed extensive tuberculosis of the intestines, especially of the jejunum and ileum and of the mesenteric glands; lungs and meninges showed no evidence of involvement. The cow died some months later, and Demme demonstrated, both macroscopically and microscopically, perlsucht.

Cases 22 to 25. Professor Demme, 1882, reports four cases of intestinal

tuberculosis which, from the family history and the clinical and pathologic evidence, he attributed to infection from milk from tuberculous cows.

Case 26. Alois Epstein,[49] 1879, reports the case of a child, three months old, in which the autopsy revealed follicular ulceration of the intestines, with involvement of the mesenteric glands and evidence of miliary tuberculosis in other organs. The author quotes Steiner and Neureiter, who, in 302 tuberculous children, found involvement of the lymphatic glands in 299 instances, and in 91 cases, or 30 per cent., the glands alone were involved. In 17 of 312 cases collected by Rilliet and Barthez there was no evidence of pulmonary lesions, and from this and a large amount of other evidence he concludes that the portals of infection may be through the digestive as well as the respiratory tract.

Case 27. Professor J. Uffelmann,[50] 1880, reports the case of a child which was fed five months with milk from a certain cow. About the seventh month the child presented symptoms of bronchial catarrh and involvement of the superficial lymphatic glands. The child died at the age of eleven months with hectic fever and abdominal symptoms. No autopsy.

The cow was found to be tuberculous. The proof is not conclusive, but Professor Uffelmann is well known as a conservative writer and teacher.

Case 28. Albert Johne,[8] 1880, reports a case in which the postmortem examination of a cow revealed extensive tuberculous deposits in the lungs and abdominal organs, which had been sent to him for inspection by the owner, who was especially interested in the result of the investigation, on account of the fact that up to within the past few weeks the cow was one of the best nourished animals in his stables, and the milk had been selected by the steward for his infant son. The family physician was at once notified of the results of the autopsy, and reported progressive emaciation and a pulmonary catarrh, which he had attributed to a recent attack of measles. A short time afterward Johne learned that the child perished from miliary tuberculosis of the brain.

Case 29. Law,[51] 1880, refers to a case reported to him by Dr. Corliss, of New Jersey. A family cow, supposed to be suffering from the lung plague, was found to be affected with tuberculosis instead, and the owner's wife (a consumptive), who had been making free use of the milk, warm from the cow, was persuaded to give it up, and underwent decided improvement.

Cases 30 to 33. Law,[93] 1883, cites two cases, daughters of a Scotch family, strong and healthy, who were brought up on milk of tuberculous cows and died of tuberculosis, while two sons in the same family who did not use the milk remained healthy. See, also, Hills and Rich in *Bulletin* 42, *Vermont Vet. Exper. Station*, p. 55.

Mr. Howe, of North Hadley, Mass., lost a son, twenty months old, from abdominal tuberculosis three months after he paid a week's visit to his uncle and had been fed with the milk of the uncle's cow. The cow was killed soon after and proved to have generalized tuberculosis. The child's sickness and wasting began a few weeks after he returned home. He had

previously been strong and healthy, as were and are his parents. (Cited by Law from *Report of Vet. Congress*, at Brussels, 1883, p. 288; also, by Nocard from *Compte rendu of Fourth Internat. Vet. Congress*, Brussels, 1883, p. 188; and by Salmon, *Bulletin, No.* 33, *Bureau of Animal Industry*, 1901, p. 21.)

Case 34. H. Meyerhoff,[95] 1884, reports the case of a child, seven years of age, of healthy parentage and with a good family history, who developed tuberculosis after drinking for a long time milk from a cow suffering with pearl disease. Although the patient had also worn some infected clothing, Meyerhoff attributes the infection to the milk.

Case 35. Demme,[48] 1886, reports the case of a boy, four months of age, who developed tuberculosis of the mesenteric glands without the slightest lesion in the intestinal walls. The child was fed on unboiled milk from a tuberculous cow, as shown by the autopsy. Tubercle bacilli were isolated from the udder, as well as from the mesenteric glands.

Among 2000 tuberculous children treated during the past twenty years at the hospital Dr. Demme, a very conservative and competent authority, reported this and the preceding cases as milk-borne infections.

Case 36. Law,[93] 1894. A child, four years old, son of Col. Beecher and a grandson of Henry Ward Beecher, died March, 1894, at Yonkers, N. Y., of tuberculous meningitis. The diagnosis was confirmed by specialists. There were no known hereditary tendencies to the disease. The certainty that he had the disease, and the inability to account for it from human agencies, led the physician to suspect the milk of two Alderney cows, on which the child had been mainly fed. The tuberculin test and postmortem showed that both animals were tuberculous.

Case 37. Sonntag, quoted by Baum,[69] page 196, reports the case of a child, aged six months, which died from tuberculous meningitis. The parents were perfectly healthy, but the child had been almost exclusively fed with milk from a tuberculous cow.

Case 38. Hermsdorf[96] reports the case of a girl, aged fourteen years, of good family history and healthy stock, who died from tuberculous laryngitis. The most extensive lesions were found in the ileum and cecum. The pulmonary lesions were slight. Inquiry revealed the fact that the girl had been in the habit of drinking the milk while still warm from a tuberculous cow.

Case 39. W. P. Northrup,[97] 1890, reports the case of an infant, aged fifteen months, which was brought to the New York Foundling Hospital when two hours old, placed with a wet-nurse, from whom it was taken in the twelfth month on account of its miserable condition, developed general tuberculosis, —primary intestinal infection—possibly from food infection.

Cases 40 to 52. Ollivier,[98] 1897, presented to the Paris Academy of Medicine, February 24, 1891, the history of twelve young ladies, scholars in the Pension of the Dames Blanches at Chartres, all suffering from tuberculosis, of whom five died, the last death from tuberculous meningitis. A few days later the milch cow was butchered and found to be suffering from tuberculosis of the udder and of the internal organs. In almost all of the cases there

was evidence of intestinal involvement, and in none of the cases was there an inherited predisposition. Professor Koch in a recent address states that Ollivier in a subsequent communication before the Academy remarked that only the servants had consumed the milk from the tuberculous cow.

Cases 53 and 54. Professor Oscar Wyss,[99] 1893, reports three cases in 123 autopsies on children, aged five and three-fourths years, six and a-half years, and two years, coming within the observation of competent clinicians during a period of three years, in which tubercle bacilli were found in the primary intestinal lesions, and all were strongly suspected of being caused by infected cow's milk.

Case 55. Gosse,[100] 1893, reports the case of his own daughter, who, up to within a year of her death, was perfectly healthy, developed tuberculosis of the intestines and mesentery, which the father traced to the consumption of raw milk from some of the cows on his own farm, which were found to react to tuberculin, and postmortem examination revealed tuberculous lesions of the udder.

Case 56. Thomas M. Rotch and E. A. de Schweinitz,[102] 1893 or 1894. The case was under the care of Dr. Rotch in the Children's Hospital in Boston in 1893 or 1894. The particulars were sent to Dr. de Schweinitz, of the Bureau of Animal Industry, by Dr. Rotch. A boy, aged seven years, had been drinking a great deal of milk from one cow for about four months before entering the hospital. The cow was found to be tuberculous, the disease being demonstrated by autopsy. The boy was a case of primary tuberculous peritonitis with effusion. Laparotory was performed by Dr. Bradford, and a large amount of serous fluid evacuated. The peritoneum was found to be thickly studded with minute tubercles, and the presence of tubercle bacilli was demonstrated. Four years after the operation the boy was found to be perfectly well, and seemed free from tuberculosis.

Cases 57 to 64. Brouardel,[105] 1894 (quoted by Harrington, *Practical Hygiene*, 1902, page 102), records the death of seven children with no hereditary taint, inmates of a convent, from tuberculosis, supposedly induced by the use of milk from a cow with tuberculosis of the udder. Another case reported by him and quoted by Freudenreich (*Les Microbes es leur des Role dans la Laiterie*, Paris, 1894, p. 45) is one in which five of fourteen girls in a boarding school became infected and died. The milk which they had used daily came from a tuberculous cow. These cases and Ollivier's collection are of special value on account of the number of persons affected who have taken the same milk, the intestinal lesions, and the demonstration of tuberculous udders.

Case 65. Law,[103] 1894, reports the case of a strong, vigorous boy, aged one and a-half years, who for a week drank the milk of a cow which was shortly afterward condemned and killed in a state of generalized tuberculosis. In six weeks the child was noticeably falling off, and in three months died, a mere skeleton, with tuberculosis of the abdomen. The father could trace no tuberculosis in his near ancestors, but the mother's father and uncle had died of it. She, herself, was in perfect health.

Cases 66 to 68. F. A. Rich,[104] 1895, reports several cases: Case 1, Mr. C., a young man of healthy parents, died of tuberculosis. Three years later Rich tested the herd of cows from which the patient had used milk plentifully, destroyed sixty-five out of seventy-four, many of which proved, upon post-mortem examination, to be affected with general and far-advanced tuberculosis. A few months later the owner of the herd developed acute pulmonary tuberculosis, and at the close of the report was in an advanced stage of the disease. Case 2, Mr. D., a young man, died of pulmonary tuberculosis. Two months later Rich tested the herd and destroyed eighty animals, nearly 90 per cent. of the herd. Several calves and hogs were found to be tuberculous from feeding upon the milk. Case 3, Miss R., using milk from a tuberculous cow, developed symptoms of pulmonary consumption. The cow was exchanged for another, and she apparently recovered. Three years later she went to live where the above-mentioned cow was still owned and milked, and in a short time developed acute miliary tuberculosis, from which she died a month later, and the autopsy revealed general tuberculosis.

Case 69. J. L. Smith,[105] November 14, 1895, reports a case of tuberculosis in which it seemed clear that the disease had been transmitted to the little one by infected milk. The child was in charge of one of the wet-nurses of the New York Foundling Asylum, and then had been partly fed on milk from a small grocery store. Dr. R. G. Freeman found no ulceration of the intestines. The condition of the mesenteric gland, that had undergone cheesy degeneration, showed that here was the oldest lesion, and it, therefore, indicated an intestinal infection.

Cases 70 to 81. H. C. Ernst,[59] 1895. Of the 1013 replies from physicians to Ernst's questions whether they knew of cases of transmission, 895 were in the negative; 8 reported transmission from mother to child; 11 reported cases of infection through cow's milk, and 16 reported suspicious cases. Of 54 replies to the same question from veterinarians, 14 reported positive cases and 9 suspicious cases.

Case 82. M. Volkoff,[109] 1895 ("Primäre Tuberkulose des Verdauungstractus," *Gazetta Bolknia*, 1895, No. 51, quoted in Lubarsch u. Ostertag's Ergeb. der Allg. Pathologie, 1899, p. 369), reports a case of primary tuberculosis of the intestinal tract, localized in the jejunum; from there it extended to the neighboring retroperitoneal and mesenteric glands and spleen. All other portions of the intestinal tract were normal.

Cases 83 and 84. Von Ruck, 1899 (quoted in Dr. Salmon's Bulletin, No. 33), reports two cases, father and child, which he considered almost conclusive. The former developed a case of acute miliary tuberculosis. The autopsy revealed no old focus in the chest or abdomen. The child, aged nearly one year, was first treated for fever and diarrhea, but later developed symptoms of meningitis, and died. The milk which the child had received came from a Jersey cow, and no other had been used up to the time the diet was changed on account of the diarrheal attack. The father had drunk from a pint to a quart twice a day, warm, at the time of milking of this cow's milk.

Upon postmortem examination of the cow there was found extensive tuberculosis in the lungs and peritoneal cavity, and the lump in the udder contained a caseous center, which, on examination, showed numerous well-stained tubercle bacilli.

Case 85. David Bovaird, Jr.,[109] 1891 ("A Case of Primary Intestinal Tuberculosis," *Archiv. of Pediatrics*, 1901, vol. xviii. p. 894), reports a case, aged three years, a patient of the New York Foundling Hospital. Family history, nothing known. No acute illness, but boy had always been weak and sickly. He was cared for outside the institution until August, 1899. The diagnosis of primary intestinal tuberculosis is based upon the autopsy findings. The oldest and most advanced lesions were in the mesenteric node. The conclusion that the intestine has been the entry-port of the infection, Dr. Bovaird thinks can hardly be questioned. It was not possible to investigate the milk supply, but the case seemed to Dr. Bovaird to deserve to be classed as one of "Fütterungs-tuberculose."

Case 86. Ebers[109] (quoted by Bovaird) reports six cases in which tuberculosis in children was attributed to the consumption of the milk of tuberculous cows. Four of these, collected by Baum, were reported by Hermsdorf, Leonhardt and Sonntag. The remaining two were reported by Johne and Prümer. All but Prümer's case have already been presented in this table.

S. Delépine, 1898 ("A Lecture on Tuberculosis and the Milk Supply," *Lancet*, London, 1898, vol. ii. pp. 733–738), refers to Dr. Simcock's work in his laboratory, who selected thirteen cases of wasting in children, due to improper feeding, out of many more in which there was no evidence of tuberculosis in the parents or in the various organs of the children as examined in the postmortem room. Dr. Simcock considered the cases free from tuberculosis, but Delépine was not quite convinced. On close examination of the mesenteric glands, two presented clear tuberculous lesions under the microscope, and five more suggested the possibility of incipient tuberculosis.

Accidental Inoculation of Man with Bovine Bacilli (by Topical Application of Cream and Milk).

Grothan,[116] 1896, reports the case of a little girl, aged six years, suffering from an eruption on the left leg, supposed to be due to ivy poisoning. This was treated at home by the topical application of fresh cream. When seen by Grothan he recognized the characteristic appearance of a tuberculous ulcer. The cow was examined, and the udder seemed normal, yet inguinal and intraperitoneal inoculation of two rabbits with a mixture of milk and cream gave positive results. The caseous material from the nodules of the girl's leg injected into the peritoneum of a rabbit produced death from tuberculous peritonitis.

Coppez,[117] 1896, reports the case of a girl, aged seventeen years, who had a wound on the palmar aspect of the third finger, which became infected with tubercle bacilli during milking. The original lesions gave rise to over thirty-five subcutaneous abscesses in different parts of the body within six months,

and subsequently more appeared, in all sixty to sixty-six. At no time could any visceral lesions be recognized, the lymph nodes of the neck being greatly enlarged; after several months death ensued.

Priester,[118] 1896, p. 11, reports the case of a young man who tried to remove a number of tattooes from his hands and forearms by introducing milk into the tattooed parts by means of needle punctures. Later there appeared on the back of both hands at points which had been so treated bright red spots the size of millet seeds, containing a yellow center. Pus was evacuated from several nodules. These were found to be lupus nodules in which giant cells were demonstrated. The diseased parts were cut out and the wounds healed without a recurrence of the trouble.

Wound Infections.

L. Pfeiffer,[110] 1885, attended, at Weimar, a veterinarian, aged thirty-four years, of good constitution and without hereditary predisposition, who, in 1885, pricked his left thumb in making an autopsy on a tuberculous cow. The wound healed, but six months later the cicatrix still remained swollen, and in the autumn of 1886 the man had pulmonary tuberculosis, with bacilli in his sputa, and death occurred in two and a half years after the wound. Post-mortem revealed tuberculosis of the joint of the wounded thumb, and in the lungs extensive tubercles and vomicæ. The joint lesions showed caseous masses extraordinarily rich in tubercle bacilli.

Tscherning,[112] of Copenhagen, 1888 (*Proceedings of Congress for the Study of Human and Animal Tuberculosis*, first session, Paris, 1888, p. 275. Cited by Law, Bujwid,[110] and Salmon), attended a veterinarian who had cut his finger in making an autopsy on a tuberculous cow. The wound healed, but there remained a swelling which soon ulcerated and refused to heal, so that the whole tumefied mass had to be cut out. The microscope revealed a distinct tuberculous process and the presence of the characteristically staining bacilli. The patient recovered without further development of the disease.

T. A. Rich,[104] 1895. (*Veterinary Magazine*, December, 1895, vol. xi. p. 729.) Mr. T. cut his finger on a spicula of bone while making postmortem examination of tuberculous cows. In a few weeks he developed a tuberculous joint and a few months later showed unmistable signs of phthisis.

M. B. Hartzell,[112] Philadelphia (American Medical Association, June 1–4, 1897), reports a case of local infection in the back of the hand in the person of a previously healthy man employed to clean cars used for the transportation of cattle; the wound was caused by a piece of broken woodwork of a car, producing a typical verrucous tuberculosis, which appeared to yield to treatment. Within a year the patient developed pulmonary tuberculosis, and finally died from general tuberculosis.

M. P. Ravenel,[114] 1897, reports the case of a veterinarian who cut the knuckle of his forefinger while making a postmortem examination of a tuberculous cow. The wound healed badly, remained swollen, and showed a decided

tendency to ulcerate. Removal of the cicatricial mass was practised and the tissues sent to Dr. Ravenel for examination. They showed typical tuberculous lesions with giant-cell formation.

M. T. Naughton,[115] of Chicago, Illinois, 1899 (cited by Dr. Salmon, *Bulletin* 33, p. 19), reports the case of a man, aged thirty-four years, with a good family history, a butcher by occupation, who on May 3, 1899, while cleaning cattle viscera, fell, and a meat hook upon which hearts and lungs are hung penetrated the right hand between the second and third metacarpal bones. A tendovaginitis with some lymphangitis of the arm resulted; made a good recovery; four months afterward an abscess formed in the axilla, which was cleaned, and tubercle bacilli were demonstrated in the broken-down gland tissues. In three months afterward, or seven months from the original accident, he died from pulmonary tuberculosis.

M. P. Ravenel,[114] 1900, reports three cases of veterinarians in the State of Pennsylvania, of local infection from wounds in the finger inoculated accidentally with bovine tuberculosis in performing autopsies. In the first case a large giant cell, but no tubercle bacilli were demonstrated in the excised portion. In the second case two guinea-pigs inoculated with a portion of the excised nodule developed a generalized tuberculosis, and in the third case Dr. John Guitéras demonstrated tubercle bacilli in the excised nodule.

Law,[113] 1901 (cited by J. J. Repp, *American Veterinary Review*, New York, 1901 and 1902, vol. xxv. pp. 624–636), reports that a young veterinary friend, who was inoculated in the hand in opening a tuberculous cow, suffered from a tumefaction of the resulting cicatrix in which tubercle bacilli were demonstrated.

M. P. Ravenel[129] reports the case of his assistant, who was inoculated with bovine tuberculosis, and from whose tissues tubercle bacilli were isolated after fifty-eight days.

C. H. H. Spronk[133] and K. Hoefnagel, 1900 and 1901 ("Transmission a l'homme, par inoculation accidentelle de la tuberculose bovine, et réinoculation experimentale au veau," *La Semaine méd.*, Paris, Ann. 22, No. 42, October 15, pp. 341–343; abstracted from *American Medicine*, November 8, 1902, p. 749), report the case of a butcher accidentally wounded, May, 1900, in the finger while assisting in inspecting the tuberculous organs of a cow. The wound healed promptly, but later the finger presented evidence of infection. In February, 1902, Professor Nareth extirpated the affected portion of the skin together with the tumefied cubital ganglia. The tuberculous character of the lesions was demonstrated by microscopic examination and by the inoculation of guinea-pigs, and an emulsion made from the spleen of one of these pigs was used to inoculate a calf previously tested with tuberculin, and the animal placed in a newly-constructed stable, with the result of producing general tuberculosis as demonstrated by the presence of giant cells and numerous tubercle bacilli. Finally two guinea-pigs which had been inoculated with material obtained from this calf died of tuberculosis.

Lassar[133] ("Ueber Impfluberkulose," *Deutsche med. Wochenschrift*, No. 40,

October 2, 1902, pp. 716–718) reports thirty-four cases of verrucose tuberculosis, following wounds in 108,000 patients, but only four of these cases were butchers. Later he examined 365 men employed in abattoirs and found seven suffering from inoculated tuberculosis, while three others he considered as possibly affected. (This shows a percentage of two to three among men employed in the abattoirs, and only one-third of one per thousand among persons otherwise employed.)

Hüls[33] ("Zur Frage der Uebertragung der Rindertuberkulose auf den Menschen, *Münch. med. Wochenschrift*, No. 24, June 17, 1902, pp. 1003 and 1004) reports the case of a wealthy miller's family, composed of the wife, five sons, and two daughters, herculean in stature, and boastful of strength and health. Consumption had never occurred in the family of either parent. Of these, all but two died from consumption within a few years, and even one of the surviving sons was treated for a tuberculous abscess of the finger. Hüls states that all these cases appeared subsequently to the introduction by the miller of a herd of Simmerthal cattle on his farm, which were nearly all infected with tuberculosis.

Krause[32] (quoted by Salmon) reports a case of a butcher, aged thirty years, with a good family history, whose duty it was to remove diseased parts of cattle killed for food. The infection was located in the right arm, and was attributed by the man to a splinter of wood run into his right thumb three years ago, and who immediately after the accident removed the hide from a sick cow. Pieces of gland and skin from the arm proved on examination to be tuberculous.

Troje,[37] 1903, reports the case of a young, healthy male, who gave no personal or hereditary history of tuberculosis. He was inoculated with bovine tuberculosis on the hand, and a typical lupus lesion developed on the site of inoculation. Subsequently the lymphatic glands which drain the involved region became tuberculous, and in the course of time many other lymphatic glands throughout the body became similarly affected.

Recent Researches with Reference to the Communicability of Human Tuberculosis to Animals.

Chaveau's experiments (quoted by Salmon[2]) show that cattle were successfully infected with human tuberculous material by ingestion, intravenous injection, and by subcutaneous inoculation.

Sidney Martin,[36] 1895 (*Report of Royal Commission Appointed to Inquire into the Effect of Food Derived from Tuberculous Animals on Human Health*, London, Part I., 1895, pp. 9–11), also obtained successful results with bovine animals by feeding sputum.

Thomassen[39] ("The Receptivity of Bovine Animals for the Bacillus of Human Tuberculosis," *Transactions of the British Congress on Tuberculosis for Prevention of Consumption*, London, July 22–26, 1901, vol. iv. pp. 21–27) reports an experiment in which a calf was inoculated in the anterior chamber of the eye with a pure culture of tubercle bacillus isolated from a case of

tuberculous arthritis in man. When killed, after six weeks, both lungs were found to contain numerous miliary tubercles and some gray fibrous tubercles of larger size. The path of infection from the eye could be traced by the lymphatic glands.

Nocard,[133] 1901 (*Press. Vét.*, Angers, vol. xxi., November 30, 1901, pp. 398–403), states that cattle are not refractory to human tuberculosis.

S. Arlong,[133] 1901 ("L'inoculabilité de la tuberculose humaine et des idées de M. Robert Koch sur cette tuberculose et la tuberculose animale," *Bull. acad. de méd.*, Paris, vol. lxv., 3 ser., xlvi., No. 43, December 24, 1901, pp. 897–911), reports experiments with three different cultures of human origin. One of these had been in his laboratory since 1896. It was capable of infecting guinea-pigs and rabbits by subcutaneous inoculations; and intravenous injection with an emulsion of this culture in a heifer calf, two sheep, and a kid conveyed the disease, as the autopsy demonstrated tuberculous lesions in all these animals.

M. P. Ravenel[122] reports having fed four calves with human sputum, and postmortem examination proved that all had become affected with tuberculosis, the lesions in two being quite extensive. His inoculation experiments in calves and cows with cultures obtained from the mesenteric glands of a child which died of tubercular meningitis proved very virulent for bovine animals.

De Jong[133] ("Experiences comparatives sur l'áction pathogène pour les animaux, notanmant pour ceux dé léspèce bovine, des bacilles tuberculeux provenant du boeuf et de l'homme") reports a series of inoculations in seven bovine animals (calves and steers); all became tuberculous by the injection of tubercle bacilli of human origin. In one of the animals the disease was serious and extended; in four others it had a retrogressive tendency, and in two it was progressive. He concludes that bacilli isolated from the human body or from sputum are capable of causing tuberculosis in cattle.

J. Orth[133] ("Ueber einige Zeit-Streitfragen aus dem Gebiets der Tuberculose," *Berl. klin. Woch.*, August 25, 1902, pp. 793–978) showed by inoculation experiments that a progressive fatal tuberculosis was produced in the animals by material originating in the human subject.

Olof Stenström[133] ("Die Tuberculose des menschen u. der Rinder," *Zeitschrift f. Thiermed.*, Band. vi. and vii., Heft 4, 1902, pp. 289–291), from his experiments, states that he found it quite easy to infect cattle with human tuberculosis.

Max Wolff,[133] 1902 ("Perlsucht und menschl. Tuberkulose," *Deutsche med. Woch.*, 28 Jahr., No. 32, August 7, 1902, pp. 566–570), reports inoculation from cases of primary tuberculosis of the intestines in man, from which he concludes that pearl disease of cattle may appear in man.

Johannes Fibiger and C. O. Jensen,[133] 1902 ("Uebertragung der Tuberculose des Menschen auf das Rinder," *Berl. klin. Woch.*, 39 Jahr., No. 38, September 22, 1902, pp. 881–886), conclude by stating that Koch announced that one could distinguish between human and bovine tuberculosis by inoculating

calves subcutaneously. If this is true, then they are of the opinion that three of the calves cited in their experiments must be considered as perlsucht, and the idea that tuberculosis of cattle is not virulent for man is disapproved.

Dean and Todd,[133] 1902 ("Abstract of Certain Experiments on Tuberculosis," *Lancet*, London, November 1, 1902, pp. 1186, 1187), from their experiments conclude that the human tubercle bacillus is by no means innocuous to the calf, as the control animal injected directly with sputum contracted an extensive glandular tuberculosis.

E. v. Behring.[133] P. Romer and G. Ruppel (*Tuberculose*, xviii. p. 90, Marburg, 1902) report experiments in which human sputum was used to inoculate a guinea-pig, and a culture from this animal's spleen was used for inoculating a goat, and an emulsion of the spleen of the goat was passed through a series of guinea-pigs, and a culture obtained from the spleen of the third guinea-pig was inoculated into a calf by intravenous injections. The calf died after four weeks directly from the tuberculosis thus produced. A cow was also inoculated November 26, 1901, with a tuberculous culture of human origin after a single passage through a guinea-pig, and on January 14, 1900, the affected eye was enucleated and a pure culture was obtained from it after one passage through a guinea-pig. The cow at the close of the report was gradually losing ground.

De Schweinitz's[133] recent experiments with intravenous injections and inoculations of cultures obtained from the mesenteric glands of children affected with tuberculous peritonitis produced fatal generalized tuberculosis in calves, and a steer inoculated subcutaneously with a piece of tuberculous tissue from one of the children also produced tuberculosis.

Mohler's[133] experiments also show "that it is not a difficult matter to obtain very virulent tubercle bacilli from human sources, and that some of these are just as virulent as bovine bacilli."

A. Cipollina[135] reports that a monkey fed with bovine milk containing tubercle bacilli cultures contracted tuberculosis, with no primary lesions apparent in the gastro-intestinal tract. On the other hand, inoculation of a calf with human bacilli resulted negatively.

Bibliography.

1. Carmichael. Essay of the Nature of Scrofula, with Evidence of Its Origin from Disorders of the Digestive Organs. London, 1810.

2. Salmon, D. E. Relation of Bovine Tuberculosis to the Public Health. Bureau of Animal Industry, Bull. No. 33, 1901.

3. Casper, John Ludwig. Characteristic der französischen Medezin mit vergleichenden Hinblicke auf die englische, 8°, pp. 608. Leipzig, 1822, p. 134.

4. See also Dupuy. De l'affection tub. Paris, 1817.

5. de Schweinitz, E. A. A Preliminary Chemical Study of Various Tubercle Bacilli. E. A. de Schweinitz and M. Dorset. Biochemical Laboratory. Science, March 6, 1903, p. 377.

6. Klencke, Ph. Fr. H. Ueber Ansteckung u. Verbreitung der Scrophelkrankheit bei Menschen durch den Genuss der Kuhmilch, 90 pp. 12°. Leipzig, 1846.

7. Klencke Mikroskopisch-pathol. Beobachtungen über die Natur des Contagiun, vi. 167, pp. 80. Leipzig, Fest, 1843.

8. Johne, Alb. Die Geschichte der Tuberculose, etc. Deutsche Zeitschrift f. Thiermed u. vergl. Pathologie, 1883, vol. ix. p. 10; see also p. 57.
9. Villemin, G. Gaz. hebdom. de méd. de Paris, 1865, vol. xxxi. p. 211; Compt. rend., 1866, vol. lxi.
10. Roustan. Recherches sur l'inculabilite de la phthisie. Paris, 1867.
11. Gerlach. Jahresb. der Thierarzneischule zu Hannover, 1869.
12. Günther u. Harms (see 11) and Gurlt and Hertwig's Mag. der ges. Thierheilk., vol. xxxvii.
13. Oesterr. Vierteljahrschrift f. wissenschaft. Thierheilk., vol. xxxi.
14. Bagge. Rep. de Thierheilk., v. Hering, vol. xxxii.
15. Zürn. Zoopathol. u. zoophysiol. Untersuchungen, 1872.
16. Bollinger. Archiv f. experiment. Pathologie, 1873, vol. i. p. 257.
17. Biffi u. Verga. Gazett. med. Ital., 1873, No. 52.
18. Bouley. Compt. rend., 1880, No. 26.
19. Aufrecht. Pathol. Mittheilungen, Magdeburg, 1881.
20. Toussaint. Rec. de méd. vét., 1880, p. 31. Compt rend., Tom. xciii., No. 5, p. 281; No. 6, p. 322.
21. Klebs. Virchow's Archiv, 1870, vol. xlix. p. 292.
22. Kitt. Ber. der Münchener Thierarzneischule, 1879–80, p. 28.
23. Semmer, Thal u. Nesterow. Deutsche Zeitschrift f. Thierm. u. verg. Path., Band. ii. p. 209.
24. Cohnheim und Salomonson. Allgem. med. Centralzeitung, 1877, No. 65.
25. Hänsell and Deutschmann. Archiv f. Opthalm., Band xxv. pp. 1 and 25.
26. Baumgarten. Berl. klin. Wochenschrft, 1880, No. 49.
27. Tappeiner. Virchow's Archiv, Band lxxiv. p. 393; Band. lxxxii. p. 353.
28. Lippl. Archiv f. klin. Med., Band xxvi. p. 523.
29. Gerlach. Archiv f. wissensch. u. pract. Thierheilk., Berlin, Band i. p. 6; see also 11.
30. Chauveau. Jour. de Méd. Vét., 1869, vol. xxv. p. 5; Gaz. Méd. de Lyon, 1870, No. 5; Rec. de Méd. Vét., 1872, p. 327: 1873, p. 929; Gaz. Hebdom. de Méd. de Paris, 1874; Bull. de l'academie de Méd., 1875, p. 891.
31. Arch. f. experim. Pathol., 1873, Band i. p. 357; Deutsche Zeitschrift f. Thierm. u. vergl. Pathol., 1880, p. 103.
32. Roloff. Zeitschrift f. pract. Vet. Wissenschaft. Berne, 1874, Band xi. p. 33.
33. Brell. Deutsche Zeitschrift f. Thiermed. u. ver. Pathol., 1877, Band iv. p. 290.
34. Metzguer. Rep. d. Thierhk. v. Hering, 1878, p. 57.
35. Langeron. Der Thierarzt, 1878, Band xvii. p. 149.
36. Blumenberg. Deutsche Zeitschrift f. Thierm. u. vergl. Pathol., 1879, vol. v. p. 319.
37. Orth. Virchow's Archiv, 1879, Band lxxvi. p. 217.
38. Lange. Deutsche Zeitschrift f. Thierm. u. vergl. Pathol., 1880, Band vi. p. 309.
39. Peuch. Compt. rend., 1879, No. 26, and 1880, vol. xc., No. 26.
40. Peuch and Toussaint. Archiv. Vétérin, 1881, No. 15.
41. Aufrecht. Med. Centralbl., 1882, p. 289.
42. Bollinger. Tagebl. der 52 Vers. deutscher Naturf. u. Aerzte, Baden-Baden, 1879, p. 264.
43. Klebs. Arch. f. exp. Pathol., Band i. p. 162.
44. Virchow. Berl. klin. Wochenschrift, 1880, vol. xvii. pp. 189–194.
45. Schoengen. Mag. f. d. ges. Thierheilk., 1873, vol. xl. p. 91.
46. Leonhardt, K. Correspondblt. d. nieder-rhein. Ver. f. öffentl. Gesundh, 1877, p. 213.
47. Bollinger and Stang. Aerzt. Intelligbl. München., January 25, 1876, xxxii. Jahr., p. 34.
48. Demme, R. 17th Med. Bericht d. Jenner Kinderspital's Bern f. 1879, pp. 27–30; also 20th Report, 1882, p. 48; also 24th Report, 1886, p. 20.
49. Epstein, Alois. Viertelj. f. d. pract. Heilk., 1879, vol. xi. pp. 103–127.
50. Uffelmann, J. Arch. f. Kinderheilk., 1880, vol. i. p. 433.
51. Law. Nat. Board of Health Bull., 1880–81, vol. ii. p. 455.
52. Creighton, C. Bovine Tuberculosis in Man. London, 1881.
53. Koch. Die Aetiologie der Tuberculose. Berl. klin. Wochen., April 10, 1882, Band xix., Heft 15, pp. 221–230.
54. Csokor. Archiv f. wissensch. u. pract. Thierheilk., 1882, p. 174.
55. Bang. Ueber Euterbuberculose, etc. Deutsch. Zeitschrift f. Thiermed. u. vergl. Pathol., 1885, p. 45.
56. Johne. Ibid., 1885, p. 18.

57. Bollinger. Ueber Tuberkelbacillen im Euter, etc. Bayr. aerzl. Int. Bl., 1883, No. 16.
58. May. Archiv f. Hygiene, 1883, Band i. p. 121.
59. Ernst. American Journal of the Medical Sciences, November, 1889, p. 439. Infectiousness of Milk: Result of Investigations Made for the Massachusetts Society for the Promotion of Agriculture. Boston, 1895.
60. Woodhead and MacFadyean. Report of British Medical Association. Dublin, 1887, No. 86, p. 979.
61. Martin. Report of the Royal Commission on Tuberculosis, April, 1895.
62. Nocard. Les Tuberculoses animales. Encycl. Scient. des aides mém., Paris, 1895.
63. Stein. Inaugural Dissert. Berlin, 1884.
64. Hirschberger. Experiment. Beitr. zur Infect. der Milch tuberc. Thiere. Archiv f. klin. Med., 1889.
65. Smith, Theobald. Misc. Investigations Concerning Infections, etc. Bull. No. 3, U. S. Bureau of Animal Industry, 1893, pp. 60–66.
66. Rabinowitsch and Kempener. Zeitschrift f. Hygiene u. Infections, vol. xxx. p. 137.
67. Dollar, J. A. W. Tuberculosis and the Milk Supply. Veterinarian, London, 1901, vol. lxxiv. pp. 393-400.
68. Kanthack and Sladen. Medical Press and Circular, London, 1899, n. s., vol. lxviii. pp. 55–57.
69. Baum, H. Gefahren d. Milchgenusses f. d. Menchen. Archiv f. Thierheilkunde, 1892, vol. xviii. pp. 187, 196.
70. Baumgarten. Ueber die Uebertragbarkeit der Tuberculose. Centralbl. f. klin. Medicin, 1884, p. 25.
71. Wesener. Kritische u. experim. Beitr. zur Lehre von der Fütterunsgstuberculose, Freiburg, 1885, pp. 49–70.
72. Fischer. Archiv. f. exp. Patholog. u. Pharmac., 1886, Band xx. p. 446.
73. Peuch. Sur la transmissibilitie de la tuberculose par le lait. Comptes rendu, T. xc., No. 26, p. 1581.
74. Ernst. See 59; also Report for the Massachusetts Society for Promoting Agriculture. Boston, 1895.
75. Falk. Ueber d. Verhalten v. Infectionstoffen im Verd. Kanale. Virchow's Archiv, 1883, Band xciii. pp. 117.
76. Zagari. Sul Passagio del virus tuberculare pel tubo degenende del cane. Giornale intern. delle Scienzeo, Med., 1889.
77. Gebhardt. Virchow's Archiv, 1890, Band cxix. p. 127.
78. Dobroklonski, v. Quoted by Bovaird and Salmon. De la pénétration des bacilles tuberculeaux dans l'organisme a traverse la muqueuse intestinale et du développement de la tuberculose expérimentale. Arch. de Méd. expér. et d'anat path., Paris, 1890, 1 ser. v. 2, pp. 253–271.
79. Desoubry, G., and Porcher, Ch. Quoted by Salmon. De la présence de microbes dans le chyle normal chez le chien. Compt. rend. Soc. de Biol., Paris, v. 47, 10 sér. v., No. 5, February 15, 1895, pp. 101–104.
80. Nicolas, J., and Descos, A. Passages des bacilles tuberculeaux après ingestion dans les chylifères et el canal thoracique. Jour. de Physiol. et de path. gén. of Paris, September 15, 1902, v. 4, No. 5, pp. 910–912.
81. Editorial, Tuberculosis and the Milk Supply. Lancet, London, 1890, 1, p. 395.
82. Günther and Harms. Jahresber. der Thierärzl. Arzneischule, Hannover, 1873, pp. 75, 107.
83. Siedamgrotzky. Tuberc. Uebertragungsversuche. Arch. f. wiss. u. pract. Thierheilk., 1882, 174.
84. Nosotti. Giornale della Societa Ital. d'Igiene, 1885, vii. 2, p. 87.
85. Schreiber. Zur Lehre von der artif. Tuberculose. Dissertation. Königsberg, 1875.
86. Lucas und Morro. Uebertragung der Rindertuberc. auf Schweine, Hühner durch milchgenuss. Berliner Archiv, 1885, p. 104.
87. Utz. Zur Fütterungstuberc. beim Schweine. Bad. Mittheil., 1888, p. 7.
88. Klebs. Die Künstliche Tuberculose. Mittheilungen, 1882, p. 20.
89. Kruckow. Ueber Tuberculose, Ibid., p. 20.
90. Pfennigwerth. Sächsischer Jahrb., 1889, p. 119.
91. Vollers. Mittheil. a. d. Thierärztl. Praxis in Preussichen Staate, N. F., Band xi. p. 101.
92. Woodward, G. Sims. Milk and Disease. Medical Press and Circular, 1888, xiv. p. 267.

93. Law. Papers and Addresses of the New York State Vet. College of 1896–98, p. 85. Quoted by Salmon, Repp, and others.

94. Demme. (See 48, Report for 1886, p. 20.)

95. Meyerhoff, H. Ueber die Contagionstät der Tuberculose. Zeitschrift f. klin. Med., 1884, vol. viii. pp. 575–579.

96. Hermsdorff. Ueber primäre Intestinal Tuberculose. Inaugural Dissertation, München.

97. Northrup. American Journal of the Medical Sciences, 1890, vol. c. p. 268.

98. Ollivier. Berliner Thierärztl. Wochenschrift, January 22, 1892, p. 42.

99. Wyss, Oscar. Corresp.-Bl. f. Schweitzer Aerzte, 1893, vol. xxxiii. p. 745.

100. Gosse. Jour. de Geneve, October 31, 1893.

102. Rotch and de Schweinitz. Quoted by Salmon. Bulletin No. 33, p. 20, Bureau of Animal Industry, U. S. Dept. of Agriculture, 1901.

103. Law. Bull. No. 65, Cornell Univ. Exp. Station, 1894. Quoted by Bovaird. Archiv. of Pæd., December, 1901.

104. Rich, T. A. Relation between Human and Bovine Tuberculosis. Veterinary Magazine, December, 1895, vol. ii. p. 729.

105. Smith, J. L. Tuberculosis Originating in Intestinal Infection. Archives of Pædiatrics, New York, 1896, vol. xiii. p. 52.

106. Brouardell. Quoted by Harrington, from Annales d'Hygiène, publ. xxiv. p. 65.

107. von Ruck. Quoted by Salmon, Bull. No. 33.

108. Hills. Bull. No. 42, Vermont Vet. Experim. Station, p. 55.

109. Prümers. Quoted by Bovaird. Archives of Pædiatrics, December, 1901, vol. xviii.

110. Pfeiffer, L. Zeitschrift f. Hygiene, 1888, Band iii. p. 209. Quoted by Bugwid, Oest. San. Wesen., Wien, 1898, x. Beil. z., No. 41, p. 7–21. Also by Salmon, Bull. No. 33, p. 17.

111. Hartzell. Quoted by Salmon, Bull. No. 33, p. 17.

112 Tscherning. Quoted by 110 and 111.

113. Law. Quoted by Repp. American Vet. Review, New York, 1901–2, vol. xxv. pp. 624, 636.

114. Ravenel, M. P. Three Cases of Tuberculosis of the Skin, Due to Inoculation with the Bovine Tubercle Bacillus. Philadelphia Medical Journal, July 21, 1900; Medicine, Detroit, July and August, 1902.

115. Naughton, M. T. Quoted by Salmon, Bull. No. 33, p. 19.

116. Grothan. Quoted from Omaha Clinic, February, 1896, by Salmon, Bull. No. 33, p. 17.

117. Coppez. Cited by Theob. Smith, Journal of Experimental Medicine, vol. iii. p. 505; also by Salmon, Bull. No. 33, p. 18.

118. Priester. Cited by Salmon, Bull. No. 33, p. 18, from the Proceedings of Congress for the Study of Human and Animal Tuberculosis, 1st sess., Paris, 1888, p. 275, and Zeitschrift f. Med. Beamte, 1896, p. 11.

119. Smith. Transactions of the Association of American Physicians, 1896, vol. ix. p. 75.

120. Smith. A Comparative Study of Bovine Tubercle Bacilli and of Human Bacilli from Sputum. Journal of Experimental Medicine, vol. iii. pp. 451–511.

121. Koch. Cited by McFadyean, Journal Comp. Pathol. and Therap., Edinburgh and London, 1901, vol. xiv. pp. 215–224.

122. Ravenel, M. P. Medicine, Detroit, July, 1902, vol. viii., No. 7, pp. 529–546; August, No. 8, pp. 617–632.

123. de Schweinitz and Mohler. Cited by Salmon in an unpublished report on Animal Diseases, submitted to the American Public Health Association (New Orleans meeting, 1903).

124. Orth, J. Cited by Salmon, ibid., from Berlin. klin. Wochenschrift, August 25, 1902.

125. de Jong, A. Cited by Salmon, ibid., from Ann. de méd. Vét., Bruxelles, 1902, vol. li., No. 4, ap., pp. 181–190.

126. Vagedes. Experiment. Prüfung der Virulenz v. Tuber-bacillen. Zeitschrift f. Hyg. und Infect., August 19, 1898, v. 28, pp. 276–320.

127. Lartigan, A. J. A Study of the Variations in Virulence of the Bacillus Tubercle in Man. Boston Journal of Medical Research, July, 1901, vol. vi., No. 62, pp. 156–162.

128. Delépine, Sheridan. British Medical Journal, London, September 27, 1902, p. 947.

129. Ravenel, M. P. Transactions of the British Congress on Tuberculosis, etc. July, 1901, vol. i. pp. 91, 92.

130. Heller. Cited by Salmon, from München. med. Wochenschrift, 1902, 49 Jahrg., No. 15, ap. 15, pp. 609–611.

131. Bovaird, D. Collection of Primary Intestinal Tuberculosis. Archives of Pædiatrics, December, 1901, vol. xviii.

132. Gottstein. Cited by Salmon, from München. med. Wochenschrift, October 8, 1901, Band xlviii., No. 41, pp. 1610–1612.

133. Salmon, D. E. Report of the Committee on Animal Diseases, submitted to the American Public Health Association, New Orleans meeting, 1903. Not yet published.

134. Jacobi, A. Notes on Cow's Milk and Infant Tuberculosis. New York Medical Journal, January 25, 1902, pp. 134–136.

135. Cipollina, A. Beitrag zu dem Studium der Rinder und menschlichen Tuberculose. Berlin. klin. Wochenschrift. Abstract in Journal of the American Medical Association, March 28, 1903.

136. Hand, Alfred, Jr. Autopsy Statistics at the Children's Hospital, with Reference to Tuberculosis and Its Etiology. Proceedings of the Pathological Society of Philadelphia, March, 1903.

137. Troje. Deut. med. Wochenschrift, March 12, 1903. Abstract in Medical Record, April 11, 1903, p. 590.

DISCUSSION.

DR. TRUDEAU: In connection with the evidence Dr. Kober and Dr. Theobald Smith have presented as to the communicability of bovine tuberculosis to the human subject, I think the work done in preventive inoculation against tuberculosis tends to bring additional proof of the genetic unity of the three types of bacilli—the avian, the bovine, and the human. The fact that I have shown the avian to protect the rabbit against the bacillus of man, and that Behring and others have immunized cows against infection by bovine tubercle bacilli by preventive inoculations of cultures of human origin, shows a very close genetic relationship between the three varieties of tubercle bacilli. The virulence of any of these varieties for any particular host is no doubt greatly modified by the kind of host to which the germ has recently become habituated. The avian bacillus is naturally pathogenic for the rabbit, but not for the guinea-pig. Yet, after passing it through several rabbits at the Saranac Laboratory, we found it then became virulent for guinea-pigs.

DR. THEOBALD SMITH: I think we all agree that the differences in the tubercle bacilli from animals and man are slight, but the question is, What is their significance? There is evidently some difference between the bovine bacillus and the bacillus of man, and it seems as though it might be summed up in the action of the bacilli upon glycerin. Such profound biologic difference would tend to separate two forms in other respects alike. Their identity is not necessarily established by their reciprocally immunizing qualities.

ON THE PRODUCTION OF SPECIFIC CYTOLYTIC SERA FOR THYROID AND PARATHYROID, WITH OBSERVATIONS ON THE PHYSIOLOGY AND PATHOLOGY OF THE PARATHYROID GLAND, ESPECIALLY IN ITS RELATION TO EXOPHTHALMIC GOITER.

By W. G. MacCALLUM, M.D.,
OF BALTIMORE.

In March, 1902, Gontscharukov, of Kiew, published a short paper in the *Centralblatt f. Allg. Pathologie* on the production of a specific antithyroid serum, in which he states that after the injection, at intervals of four weeks, of an emulsion of dogs' thyroids into the subcutaneous tissues of a sheep he was able to produce in other dogs, by the injection of the serum of this sheep, which died during the experiment, certain tetanic symptoms which he thinks indicate the existence of a specific antithyroid toxin.

Knowing the literature on the physiologic properties of the parathyroid glands as contrasted with those of the thyroid, it seemed desirable to control these results, and part of the following pages will be devoted to the experiments carried out with this in view.

Briefly stated, it has been shown[1] that the destruction of the thyroid alone produces disturbances of metabolism, which appear slowly and gradually lead to cachectic conditions—the so-called myxedema. Destruction of the parathyroid alone, on the other hand, produces the acute, rapidly fatal nervous phenomena which have so long been thought to be due to the extirpation of the thyroid. The most evident symptoms in this condition are the tetany and polypnea which rapidly exhaust the animal. The confusion which has so long existed

[1] For a discussion of this subject, with full analysis of literature, see Jeandelize, Thèse de Nancy, 1902. Insuffisance Thyroidienne et Parathyroidienne.

as to the relation of these symptoms to the thyroid depends on the fact that the parathyroids have only recently been discovered, and that, being small and inconspicuous organs often embedded in the surface of the thyroid, they have usually been removed with the thyroid; hence the so-called early symptoms of thyroidectomy, which produce their fatal effect before the true symptoms of thyroidectomy have had time to develop.

It was, therefore, proposed to attempt the production of a specific cytotoxin for the thyroid alone and similarly a specific cytotoxin for the parathyroid alone, and to compare their effects. Now, since the parathyroids are so small, it is necessary to choose some animal which is slaughtered in great numbers for the experiment, so that a quantity sufficient for immunization of another animal may be obtained. Besides this, it is important that the animal from which the parathyroid is obtained should be small enough to be affected by a reasonable amount of serum which might be obtained from the immunized animal. Dogs were, therefore, chosen, since they vary much in size and are slaughtered in great quantities in the dog pounds. For immunization the goose was chosen as an animal widely separate from the dog and highly resistant to infection. The thyroids of large quantities of dogs were obtained aseptically, and with the same precautions the parathyroids were separated from them and emulsions of each organ were injected separately into the peritoneal cavities of geese provided for the purpose.

The process of immunization may be represented for convenience by the following table:

Date.	Goose 1, injected with thyroids of	Goose 2, injected with thyroids of	Goose 4, injected with parathyroids of
December 13	4 dogs.	.....	.....
" 18	4 "	.....	.....
" 24	4 "	.....	.....
" 31	4 "	.....	.....
January 16	4 "	.....	.....
February 17	10 "	15 dogs.	30 dogs.
" 25	.....	9 "	9 "
" 28	15 dogs.	25 "	43 "
March 8	.....	35 "	46 "
" 18	22 dogs.	22 "	30 "
" 31	.....	39 "	39 "
April 8	.....	40 "	40 "

From this table it will be seen that in each instance a very large quantity of the organ in question has been injected into the perito-

neum of the geese at relatively short intervals. They showed absolutely no ill effects of this treatment and are quite well to-day. Blood was taken at various times from veins in the wings, received aseptically, defibrinated and centrifugalized, and the sterile serum used for injection into a series of dogs, as will be seen from the following table and from the descriptions of the experiments. In some instances one injection only was made, in other cases two or three or even five injections were made at intervals, usually into the peritoneal cavity. Several of the dogs were killed after varying periods in order to study the histologic changes in the thyroids, even although symptoms may not have developed. In one or two cases the animals died of peritonitis or of pneumonia.

Dog No.	Date of injection.	Date of death.	Amount of serum injected.	Results.	Duration of exp. in days.	Histologic condition of thyroid.
1	Jan. 6 Feb. 10	Feb. 17	5 injections of 1–5 c.c. per kilo.	Emaciation; cachexia; conjunctivitis; death.	41	Normal
2	Jan. 6 " 13	Jan. 20	2 injections of 1–4 c.c. per kilo.	Killed; no symptoms.	14	Festooned and hypertrophied.
5	" 27	Feb. 26	1 injection of 5 c.c. per kilo.	Emaciation; cachexia; conjunctivitis; death; pneumonia.	30	Normal.
7	Feb. 3 " 21	" 22	2 injections of 5 c.c. per kilo.	Death, of peritonitis; no symptoms; slight emaciation and cachexia.	19	Normal.
8	" 3	" 6	1 injection of 5 c.c. per kilo.	Dog killed; no symptoms.	3	Normal.
9	" 10 " 21	" 25	2 injections of 5 c.c. per kilo.	Emaciation; cachexia; convulsive movements; pneumonia.	14	Degenerated and disintegrated.
10	" 10	" 18	1 injection of 5 c.c. per kilo.	Dog killed; no symptoms.	8	Normal.
11	" 21	" 28	1 injection of 5 c.c. per kilo.	Prolapse of rectum.	7	Normal.
12	" 27 April 7	Still alive	2 injections of 3–5 c.c. per kilo.	No symptoms.		
13	Feb. 27	April 5	1 injection of 5 c.c. per kilo.	Emaciation; cachexia(?)	6	Normal.
15	March 7 " 12 " 24	Mar. 26	3 injections of 5 c.c. per kilo.	Emaciation; urinary changes; death from peritonitis.	20	Normal.
19	April 11	April 12	1 injection of 5 c.c. per kilo.	Killed for comparison of thyroid extirpated before injection with the remaining one.	1	Both thyroids normal.
20	" 23	" 25 " 29	1 injection of 10 c.c. per kilo.	Thyroids extirpated; one after two days, the other after six days.	2–6	Both thyroids normal.

In most of the others, which were kept until they died, a marked emaciation appeared, with symptoms which might be considered as the expression of a general cachexia. In one instance only were there convulsive movements of the muscles.

Thus from the table it will be seen that Dogs 1, 5, 7, and 9 showed definite emaciation, with symptoms of cachexia; conjunctivitis and furuncles on the skin, with some anemia, were the most noticeable things, and these to a less degree were present also in Dogs 13 and 15. In all but No. 1, however, death seems to have been directly due to some intercurrent affection. The convulsive movements seen in Dog 9 had not exactly the type seen usually after extirpation of the parathyroids, but were rather choreiform in character. It is difficult to find a satisfactory explanation for them.

The condition of the thyroid histologically in all of these dogs excepting Nos. 2 and 9 was practically the normal. No definite departure from normal could be made out in the cells nor in the alveolar contents. In No. 2 there occurred the curious condition of enlargement of the cells which become elevated into folds and papillary projections such as were described by Dr. Halsted in the regenerative hypertrophy of the thyroid after partial extirpation. Since this condition occurred but once in the series, and since it has been found several times in the thyroids of the dogs killed at the pound, it seems probable that this is merely an accidental occurrence here. In the thyroid of Dog 9 marked disintegration of the epithelium, with loss of colloid, was actually found.

Dogs 2, 8, 10, 19, and 20 were killed or had the thyroid extirpated after the lapse of periods of one, two, three, six, eight, and fourteen days from the time of injection of the serum. In none of these were there any symptoms whatever, and in every one the thyroid was found to be histologically quite normal.

From these latter experiments it seems quite evident that whatever the properties of the serum of the immunized animal it does not effect any injury to the thyroid cells *in situ* which is visible to the eye in the microscopic preparation; nor in those dogs which were allowed to live as long as they would was any definite or constant lesion found in the thyroid tissue which could be ascribed to the serum, unless it be the disintegration found in the thyroid of Dog 9.

Nevertheless, with the exception of Dog 12, which is still alive and well after repeated injections, several of these dogs became emaciated and subject to intercurrent affections. By way of control two dogs were injected with similar quantities of normal goose serum. Of these, one became emaciated and died without evident lesions after twenty-two days; the other showed no symptoms and is still alive. It seems pos-

sible that the emaciation may be due to the hemolytic effect of the serum, but if the test-tube tests of the hemolytic power of the specific serum can be applied to the behavior in the dog's body, a calculation will show that only a very few cubic centimeters of blood will be destroyed by the amount injected.

It is possible, of course, that the emaciation and cachexia may be due to a specific action of the serum injected, perhaps by its combination with the specific secretion of the thyroid without any actual destruction of the cells, but merely the neutralization or elimination of the secretion. Certainly, as shown by the series in which the dogs were killed, the serum does not produce a histologic lesion so severe that it could not be entirely recovered from by the hyperplasia of adjacent cells long before any symptoms could arise from thyroid insufficiency. Indeed, the extreme cachexia and emaciation of these dogs led to their death before the first symptom should appear in a dog which had been deprived of the thyroid gland by operation without injuring the parathyroid. Injections of the serum of Goose 4 immunized from the parathyroids of dogs were made in a smaller series, as follows:

Dog No.	Date of injection.	Date of death.	Amount of serum injected.	Results.	Duration of exp. in days.	Histologic condition of parathyroid.
3	Jan. 6 Feb. 10 April 7	Still alive.	1, 2, and 5 c.c. per kilo.	No symptoms: dog still alive.	125	
16	Mar. 11 " 24	Mar. 26	2 injections of 8 c.c. per kilo.	Emaciation; slight twitchings; conjunctivitis; death from pneumonia.	15	Normal.
17	" 28	April 2	1 injection of 6 c.c. per kilo.	Emaciation; conjunctivitis.	5	Normal.

A priori, more might be expected from the destructive action of an antiparathyroid serum than from the antithyroid, because the symptoms and results of a destruction of the parathyroid appear so much more quickly and are so much more intense than those which result from thyroidectomy. The above table, however, does not seem to show that any definite results have been obtained by the injection of this serum. One dog is still alive and shows absolutely no effect; the other two died after a number of days, in which they became much emaciated. In No. 16 there were convulsive twitchings of the muscles but no dyspnea. It is possible that these twitchings were in this case the expression of a parathyroid insufficiency, and that the serum had merely neutralized the normal secretion of the parathyroid suffi-

ciently to allow of this development. In both of these cases, however, the parathyroids were histologically normal.

If any conclusions, then, can be drawn from these series of experiments they would be that the attempt to produce a cytotoxin capable of destroying the cells of the glands *in situ* has not been successful, but that we may possibly believe that a material has been produced in the blood of the goose which will combine with the normal secretion of the dog's thyroid or parathyroid and neutralize it, thus allowing the symptoms which ordinarily follow extirpation of these glands to occasionally appear in a mild degree. It can hardly be thought, however, that the cachexia and emaciation which appear in almost all of these dogs, and even in those injected with normal goose serum, are dependent entirely upon the specific nature of the serum.

These experiments throw considerable doubt, therefore, upon the results obtained by Gontscharukov and especially upon his interpretation of them, for in any case one should not expect tetanic contractions as an effect of the destruction of the thyroid by a specific serum.

In the course of these experiments the interest of the writer became more strongly attracted to the problem of the nature of the parathyroid glands and their function in the body and rôle in disease, and since the production of a specific cytotoxin was so unsatisfactory, an attempt was made to further the knowledge of these glands by experimental and operative methods.

The history of the experimental investigations into the nature and functions of the thyroid is a long and familiar one, but that concerning the parathyroid is limited to the years since their discovery by Sandström[1] in 1880 and their rediscovery by Gley[2] in 1892. Since that time a number of French and Italian workers have added greatly to the knowledge of these bodies, and several recent papers have reviewed the whole subject, with full literature references. Especially noteworthy among these are the papers of Welsh,[3] Benjamins,[4] and Jeandelize.[5]

For years it had been noted that after thyroidectomy in certain animals there occurred symptoms of the most acute and intense kind, which led very rapidly to the death of the animal; while in other ani-

[1] Upsala. Läkare förenings Förhandlingar, 1880.
[2] Archives de Physiol., 1892.
[3] Journal of Anatomy and Physiology, 1898, vol. xxxii.
[4] Ziegler's Beiträge, 1902, Bd. xxxi.
[5] Loc. cit.

mals the same operation was attended by no serious consequence in adults or led in young animals after a long time to nutritive disturbances, changes in the skin, and interference with growth—in a word, the symptoms known as myxedema, which are analogous if not entirely identical with those of cretinism. There was much difficulty in the explanation of this difference in different animals, but it was observed that the so-called acute symptoms of thyroidectomy came on in carnivorous or omnivorous animals, while in those animals whose food was largely of a carbohydrate nature—the herbivora and certain rodents—such symptoms were not found, and it was thought that the excess of nitrogen in the food of the carnivora was the cause of the symptoms of acute poisoning. Restriction of these animals to a carbohydrate diet did indeed seem to moderate the violence of the symptoms, if it did not entirely preclude them,[1] but the difficulty was practically cleared up by Gley,[2] who showed that in rabbits which were thought to be immune from such acute symptoms the same clinical picture could be produced if instead of the ordinary extirpation of the thyroid, one also extirpated the parathyroids, which lie so far away from the thyroid as to be always left behind in the usual operation. The parathyroids were thus shown to be organs of great importance. Gley found that they became enlarged if they were left and the thyroid excised, and he therefore thought that they should be considered as portions of the thyroid which had remained in the embryonic state, and which on the expiration of the thyroid underwent such an hypertrophy as to compensate for the lost thyroid. This view, however, was soon disproved by the researches of other writers, among whom Kohn[3] may be mentioned. Gley found that the separate extirpation of thyroids and parathyroids in adult rabbits were alike unproductive of acute symptoms, but when both were excised—even although at widely separate operations—the tetany resulted very soon after the last operation. This seemed to support his idea that the parathyroids were merely embryonic structures ready to supply the place of the thyroids. It was soon discovered, however, that there are four parathyroids in the rabbit, and that in extirpating the two distant glands and leaving apparently only the thyroid Gley was really leaving also the two parathyroids which are intimately associated with the thyroid. After this discovery it was found that the complete

[1] Verstraeten u. Vanderlinden. Memoires de l'acad. de med. de Belgique, 1890.
[2] Loc. cit.
[3] Archiv f. Mikr. Anat., 1884 and 1896, Bd. xliv., xlvi.

extirpation of the parathyroids alone produces acute tetanic phenomena, while the extirpation of the thyroid alone still produces only the chronic cachexia.

Various detailed studies of the results of complete and partial parathyroidectomy have since been made, and the names of Moussu,[1] Vassale and Generali,[2] Lusena[3] and others should be especially mentioned in this connection. Much confusion has arisen from the fact that in much of the work the thyroid has been extirpated as well as the parathyroid, and this has stimulated inquiry into the relation of these glands to one another, a question which is still far from definitely settled. It was stated by Gley that the parathyroids become enlarged after extirpation of the thyroid, and this has been confirmed by several authors; but Moussu has pointed out that this is no doubt due to the extirpation of two of the parathyroids with the thyroid, so that the hypertrophy is to compensate for them and not for the thyroid. There is no histologic proof that parathyroid tissue can ever become converted into thyroid tissue, and there is now a general agreement of opinion that the glands are organs of very different nature. Moussu, however, holds that there is a functional relationship between them, and this idea is supported, by the discovery by Gley of iodine in their substance, by the statement that thyroidectomy lessens the violence of the tetany which follows parathyroidectomy, and that the thyroid undergoes some alterations after parathyroidectomy.

The object of this investigation was mainly to determine, if possible, the rôle of the parathyroid glands under normal conditions. In extirpating these organs from dogs and observing under various conditions the results, a beginning has been made and a number of the observations mentioned above confirmed; but much work, largely of a chemical nature, must be done before we can be said to possess any very clear light on the subject. Nevertheless, since the literature on the subject is still small and nothing seems to have been published in this country, it has seemed permissible to publish here these results, in the hope that they may at least attract attention to this organ, which is without doubt of considerable importance in the animal economy. Dogs were used in these experiments and the operations carried out under aseptic precautions. Wound healing was usually

[1] C. R. Soc. de Biol., 1892, 1893, 1897, 1898.
[2] Riforma Medica, 1897, vol. i., ii., iii.; Arch. ital. de Biol., 1900, vol. xxxiii.
[3] Riforma Medica, 1898, vol. iv.; 1899, vol. ii.

good. The nature of the experiments and the results may be briefly set down in the following table:

Dog No.	Date of operation	Date of death.	Operation.	Symptoms.	Anatomic results.
104	Mar. 14	Mar. 18	Parathyroidectomy.	Tetany, dyspnea, epileptiform convulsions, sialorrhea	Thyroid normal.
106	" 12	April 5	Partial parathyroidectomy.	Emaciation, diarrhea.	Thyroid normal; slight folding of epithelium.
107	" 24	May 22	Partial parathyroidectomy March 24th. Excision of left thyroid and remaining parathyroid May 6th.	No symptoms.	Portion of parathyroid left embedded in thyroid.
109	" 31	April 3	Parathyroidectomy, sciatic cut during tetany; spinal cord cut during tetany; dog bled and transfused into another dog.	Violent tetany, polypnea 200 c.c.; no abatement of spasms; exophthalmos.	Thyroid normal.
110	April 2	" 10	Thyroparathyroidectomy.	Slight twitching; emaciation; cachexia.	
111	" 2	" 13	Parathyroidectomy and operation for same; sciatic cut; only two parathyroids removed in all.	No symptoms.	
113	" 10	" 20	Parathyroidectomy; sciatic and crural cut; parathyroid injection April 15th.	Tetany April 15th; No twitching in paralyzed leg; tetany continues.	Anterior horn cells show chromatolysis.
114	" 15	.....	Thyroidectomy; two parathyroids left.	No symptoms.	Urinary changes.
115	" 18	April 21	Parathyroidectomy; nerves to leg cut.	Tetany; exophthalmos; Cheyne-Stokes respiration; tachypnea; no twitchings in paralyzed leg	Anterior horn cells and pyr. cells of cortex show chromatolysis and swelling of nucleus.
116	" 21	" 29	Parathyroidectomy.	Tetany, tachypnea, etc.	Urinary changes.
117	" 25	.....	Parathyroidectomy; injection of parathyroid.	Twitching seems to have been stopped.	Still alive.
118	" 28	.....	Partial parathyroidectomy.	No symptoms.	
119	" 28	.....	Partial parathyroidectomy; infusion of blood from No. 121.	No symptoms.	
120	" 23	May 9	Injection of goose serum; thyroparathyroidectomy; transfusion of normal blood; bleeding, and infusion of salt solution several times.	Tetany disappears after transfusion; cachexia.	
121	" 30	" 3	Parathyroidectomy; transfusion of blood to No. 119.	Tetany, etc.	
123	May 5	.....	Parathyroidectomy; partial thyroidectomy.	No symptoms.	
124	" 6	" 9	Parathyroidectomy; section of spinal cord; transfusion of blood.	Tetany in non-paralyzed part.	
125	" 6	.....	Parathyroidectomy.		
126	" 7	" 9	Parathyroidectomy.	Tetany.	
127	" 9	.....	Parathyroidectomy; infusion with blood of No. 124.	No symptoms: death during night	

The condition into which these parathyroidectomized animals fall after a few days is about as follows: Beginning with symptoms of unrest and anxiety, with slight twitchings of the muscles here and there and fibrillary tremors of the tongue, the animal rapidly passes into a state in which the most violent tetanic spasms of all the muscles occur. The dog is able to walk at first but rather stiffly, the hind legs being especially awkward and beyond his control; frequently with a sudden twitch they slip from under him and bring him down upon the floor. Sometimes in walking about or climbing up stairs the dog suddenly falls to the floor in an epileptiform convulsion—the legs are stretched out rigid, the head stretched forward, all the muscles of the neck being thrown into a tetanic contraction—breathing stops for a few moments and is then gradually resumed, the legs finally relax, and the dog recovers and walks about again. Usually, however, the onset of the tetany is more gradual and continuously progressive, and from the condition in which spastic walking is possible the dog goes on to that stage in which with all the muscles rigid and twitching violently he is unable to stand at all. The most violent trismus, with snapping of the jaws, appears, and the tongue is bitten through and through; saliva pours from the mouth; all the facial muscles twitch, and the eyes project from the fact that the upper lid is much retracted. Respiration is profoundly affected, and the dogs appear to stretch out their heads, panting for breath. The rate of respiration is greatly increased, even up to 200 or 250 per minute, and with the violent panting the dog struggles about, drooling saliva and jerking convulsively in every muscle. With this there is no sign of cyanosis, and the blood is readily arterialized by shaking up in the air. The tachypnea cannot, therefore, be readily explained as due to lack of proper oxygenation, or air hunger. Sometimes it is very irregular. and varies in the fashion described as Cheyne-Stokes respiration.

Exhaustion soon supervenes, and the convulsions become less violent and the respiration less rapid, so that if the animal does not die in the height of the attack he lies relatively quiet for a time before death. During this series of phenomena the heart beat is not notably increased in rate; the initial shock is somewhat sharp and the curve high, but there are no marked changes. The temperature is said to rise markedly with the tetany and fall again on its disappearance. Sensation seems to be much dulled if not quite lost during the tetany.

Several problems in connection with this phenomenon, therefore, present themselves: 1. Are we dealing with a condition in which there is lack of some necessary secretion of the parathyroid? 2. Is there, on the other hand, a poison produced somewhere in the body which is circulating in the blood and producing these phenomena, but which, in the normal animal, would be neutralized either by the parathyroid cells themselves or by their secretion? 3. Is this poison produced by the metabolism of any particular group of cells, or, in other words, are there specific relations between the parathyroid and any other particular organ; for example, is this poison directly absorbed in the intestine, or is it the waste product in the metabolism of the muscles or the noxious excretion from the metabolic processes in the nerve cells themselves?

The first of these questions seems not especially difficult to approach. If the parathyroid be conceived of as producing a secretion necessary to the functions of the body, the effects of the lack of this secretion—which must be carried about in the blood, since there is no other outlet—should not be ameliorated by the removal of the blood or its dilution. In order to determine this point the blood of a normal dog was transfused directly into the veins of Dog 120, which, after removal of both thyroids and parathyroids, had reached the condition of violent tetany. The result was the complete disappearance of all tetanic symptoms after about four hours, and next day the dog seemed quite well. It might be objected that in so doing we injected with the blood of this normal animal the circulating secretion of its parathyroid. The next day, therefore, when the effect of this transfusion of blood had apparently passed off and the dog was again plunged into violent tetanic spasms, instead of transfusing normal blood the animal itself was bled and a somewhat larger quantity of normal salt solution (150 c.c.) allowed to run into the veins. The same immediate, or almost immediate, amelioration of the symptoms, with complete disappearance of the tetany, followed. Next day the tetany had reappeared, and the bleeding and infusion was again carried out with success; so, also, upon the next day, although the dog had by this time become very weak and the tetany very slight; 50 c.c., therefore, of blood were removed and 200 c.c. of salt solution infused. The result was the immediate improvement of the dog, so that he could run about. After this there was, strangely enough, no recur-

rence of the tetany, and the animal passed gradually into a cachexia, due, perhaps, to the thyroidectomy, and died after several days. Similar results have been obtained by Lusena and others. The idea that the parathyroid is active chiefly in neutralizing some toxin seems, therefore, more plausible, although it is, perhaps, not absolutely proven by this experiment.

No special light seems to be shed upon this point by the observations of various authors (Lusena, Vassale and Generali, Moussu, and others) that the tetany may be stopped or prevented by the injection of emulsions of the parathyroid gland. This corresponds obviously with the transplantation of the gland, and is analogous with similar experiments made with the thyroid. In two of our dogs (Nos. 115 and 117) it was possible by the intraperitoneal injection of an emulsion of the crushed parathyroids of the ox filtered through a cotton cloth, so as to exclude large fragments, to cut short tetanic attacks already begun and to postpone by many days the fatal result; and Lusena has been able to keep dogs alive for a long time by such a process. This shows, at any rate, that it is not necessary that the gland should be intact and in its normal connection with the bloodvessels in order to carry out the function, but that the extract is quite as efficient as long as it lasts.

Verstraeten and Vanderlinden have shown that the tetany is less violent and appears later when the dogs are kept on a milk diet than when given a diet of pure meat, which, perhaps, adds support to the idea that a poison is produced in proteid metabolism. In order to control this, one parathyroidectomized dog (No. 125) was fed exclusively on bread and water after the operation, and in this case no tetany developed within the twenty days that the dog lived. One such case, however, is very inconclusive, since one is never absolutely sure of the completeness of the operation. Again, it has been observed (Vassale and Generali, Lusena) that the tetany resulting from the extirpation of the parathyroids alone is far more intense than in those cases in which the thyroids were also extirpated, and Lusena has even shown that the tetany, once begun, can be made to disappear by removing the thyroids. Vassale and Generali explain the milder results of thyroparathyroidectomy on the ground that removal of the thyroid decreases the proteid metabolism, and hence decreases the amount of poison thrown into the circulation and ordi-

narily neutralized by the parathyroid. Lusena objects to this explanation, however, on the ground that the ameliorating effects of thyroidectomy come on at once, and that they do not follow a partial thyroidectomy. His observation that the tetany, once started, can be cut short by thyroidectomy has not, however, so far as we can ascertain, been confirmed, and his explanation of the phenomena seems, therefore, not very strongly supported. This explanation is based on the idea that the functional relationship between the thyroid and parathyroid is very close, and that the symptoms of parathyroidectomy are chiefly due to the removal of the influence of the parathyroids from the thyroid.

In two of our dogs (No. 110 and 120) we have not been able to confirm these results, for in these the tetanic convulsions appeared in both instances two days after the operation. As yet we have not had an opportunity of repeating Lusena's experiment in removing the thyroids during the tetany of parathyroidectomy.

It may be said, therefore, that while it seems improbable that the parathyroids secrete a necessary material which is circulated in the blood, the lack of which produces the disturbances described, it does seem probable that they produce a material which neutralizes poisons produced elsewhere—poisons which, if not so neutralized, may be mechanically washed out with the relief of the symptoms. Of course, it may be claimed that the parathyroid secretion is necessary to the metabolism of, say, the nerve cells, that without it the perverted or incomplete metabolism throws the nerve-muscle apparatus into the tetanic state described; but since this must be due to the presence of stimulating materials, it forms only an example of the neutralization idea in which the metabolism of the nerve cell is particularly concerned.

In order to approach this point more closely it was determined to transfer the blood of an animal in tetany into the veins of another animal. Several experiments with this end in view were therefore made. In one the blood—about 50 c.c.—was injected into the peritoneum of a small dog, but without any effect. In another case the test dog was first partially parathyroidectomized, and then, under ether, the aorta of a parathyroidectomized dog in violent tetany was connected by canulas and a rubber tube with the jugular vein of the test dog, and the full stream of blood from the aorta allowed to pour into the jugular vein until the tetanic dog was dead and blood had

ceased to flow or flowed only very slowly. The jugular vein was then ligated and the wound closed, and the dog allowed to recover from the ether. Although it was carefully watched, no signs of tetany developed. It seemed probable that in this dog enough of the parathyroid had been left to carry out the function of neutralization of the supposed poison. In the next case, therefore (Dog 127), complete parathyroidectomy was performed, and the dog, which weighed about 3000 grams, bled 100 c.c., and then only was the canula from the aorta of Dog 124, at that time in violent tetanic convulsions, tied into the jugular vein and the aortic blood allowed to flow into that vein until Dog 124 was dead; even so, absolutely no signs of tetany developed during the next forty-eight hours, and the dog died some days later, during the night, without having at any time exhibited any tetanic symptoms. It seems possible, however, that even in this case sufficient of the secretion of the parathyroids was present in the remaining blood and in the tissue juices of this freshly parathyroidectomized dog to neutralize whatever poison was introduced with the blood of the tetanic dog, so that the most that might be expected would be the somewhat earlier development of the tetanic symptoms due to the parathyroidectomy of this animal itself. Baldi[1] has in the same way injected the blood of thyroidectomized animals in the tetanic state without any result. The experiment, therefore, seems entirely inconclusive as to the question of the presence of a poisonous material in the circulating blood of a tetanic animal.

It seemed, then, of interest to localize a little more definitely the point of attack of this hypothetical poison, to determine whether the twitching of the muscles was due to the effect of some material on the muscles themselves or to an affection of the nervous system, and if the latter, of which part of the nervous system.

It was noticed that the administration of ether abruptly stopped the tetany and the tachypnea, the respiration returning to normal, but being very apt to cease abruptly, causing the death of the animal. This is perhaps to be explained by the idea that the respiratory centers are fatigued by the extraordinary dyspnea, and any depression of reflexes allows them to cease their function.

More accurate localization seemed, however, to be obtained from the following experiments:

[1] Arch. ital. de Biol., vol. xxxi. p. 281.

In one dog (No. 111) the sciatic nerve was cut at the time the parathyroidectomy was performed; in others (Nos. 113, 115) the sciatic, anterior crural, and obturator were cut. In these dogs, especially in No. 115, in which, after the intra-abdominal section of the anterior crural and obturator and the very high section of the sciatic paralysis of the leg was complete, it could be easily observed, when the convulsions appeared, that while the muscles of the other leg were in violent spasmodic contractions the paralyzed muscles lay perfectly quiet. There is a thrill which can be felt in the tetanic limb, even when more violent contractions are not actually present for the moment, which is quite absent in the paralyzed leg. The effect, therefore, is not on the muscles themselves, but rather to be localized in the central nervous system. In another dog (No. 124) the spinal cord was cut through at about the sixth dorsal vertebra and parathyroidectomy performed. The dog was, of course, completely paralyzed in the posterior part of the body; there was incontinence of urine, continual dribbling from a distended bladder, etc., and flaccidity of the extremities. Reflexes and muscular power were still present there, however; scratching in the inguinal region produced movements of the tail and pinching of the deep muscles produced movements of the legs. Three days after the operation for parathyroidectomy the dog was found in tetany. No dyspnea or tachypnea, but the forelegs were held perfectly rigid, with occasional well-marked clonic spasms. All the muscles of the anterior part of the body were in violent twitching motion; trismus and fibrillary twitchings of the tongue were observed. The posterior portion of the body was far less violently convulsed than the anterior—indeed, the twitchings seemed to stop sharply at the middle of the body—the tone of the muscles in the hind legs was lost to a great extent, and the limbs had none of the rigidity seen in the forelegs. There were, however, slight visible tremors which showed through the skin by the slight spasmodic elevations and movements of the hair.

It is, of course, impossible to draw definite conclusions from one such experiment; but it seems at least to indicate that the stimulation is not chiefly a stimulation of the anterior horn cells of the cord, but that the upper motor neurons are also and perhaps chiefly affected, for were the lower motor neurons independently affected, one sees no reason why violent spasms of the hind legs should not occur in this case, in which the connections with the cord are still intact.

The histologic examination of the spinal cord and cerebral cortex in these cases has failed to show us any such degeneration of tracts in the cord as has been described by Vassale and Donaggio,[1] but there are evidences of swelling of the nucleus of the anterior horn cells and of the cells of the cortex, with chromatolysis, as shown by the method of Nissl. These correspond in every way with the acute degenerative changes described in so many toxic conditions. The further study of these changes will be reported at a later date.

In several of these dogs in which parathyroidectomy had been performed, with death from the usual symptoms, as well as in others in which thyroparathyroidectomy and thyroidectomy alone were carried out, attempts were made to study the changes in metabolism as evidenced by the output of nitrogen in the urine. The analysis of the urine was made by Dr. Slemons, of the Johns Hopkins Hospital, and will probably be published later by him in detail with the charts of the observations; but, roughly speaking, it may be stated that in the cases of parathyroidectomy practically no changes in the nitrogenous content of the urine could be made out, while in the cases of thyroparathyroidectomy, and in the case of simple thyroidectomy in which two of the parathyroids were left *in situ*, marked alteration occurred, consisting in a diminution in the amount of nitrogen in the urine, with alteration of the relation normally existing between the compounds that go to make up this.

A summary of the results of these cases, rough as the estimations were, still serves to show that there are distinct differences between the effects of parathyroidectomy and those of thyroidectomy or of thyroparathyroidectomy, as follows:

After parathyroidectomy the ammonia is slightly increased just after the operation, with speedy return to normal. Other nitrogeneus elements show no change.

After thyroidectomy the ammonia is primarily diminished, then markedly increased; urea is decreased, amido-acid nitrogen increased, and the nitrogenous compounds precipitated by phosphotungstic acid increased.

Together with the results of other observations this tends to show that while the thyroid gland has a definite and marked influence upon

[1] Arch. ital. de Biol., 1897, vol. xxvii. p. 124.

the course of metabolism, the function of the parathyroid is directed to a different purpose, and is not specially concerned with metabolism.

It is interesting to note that in daily observations of the urine of Dog 15 in the preceding series, in which a specific antithyroid serum was several times injected, there was after each injection a temporary alteration in the nitrogenous constituents of the urine which corresponded in every way with that observed after thyroidectomy.

In the course of these experiments the idea naturally suggested itself that there might be some disease analogous in its symptoms to those produced by the extirpation of these glands, and the symptom-complex of exophthalmic goitre, with all its difficulties of explanation, presented itself at once as at least somewhat similar. Perusal of the literature showed that this idea had been put forward by Gley[1] and acted upon by Moussu,[2] who treated a case of exophthalmic goiter with the parathyroids of the ox. Moussu reports a marked improvement in his case, which was, however, unfortunately carried off by tuberculosis during the treatment. Since that time there has apparently been no attempt made to treat this disease with the parathyroid extract.

When we compare the symptoms of exophthalmic goiter with those following extirpation of the parathyroids we do find certain analogies, but they are, after all, not so striking as they might at first glance seem.

Tachycardia, so constant in the one condition, is not found in the other; the tremor in the one is represented by the violent convulsive movements of the other. Exophthalmos is sometimes approached, if not actually well developed, in dogs. Partial parathyroidectomy in dogs produces no symptoms unless under the stress of some physical strain, such as lactation, when the symptoms (Vassale[3]) are those of complete parathyroidectomy. Still we must remember, if we think of exophthalmic goiter as due to a parathyroid insufficiency, that it cannot be entirely analogous in any way to the effect of extirpation of the parathyroids in the dog, for there, instead of a gradually progressing disease, we have the acute and fatal results of a complete extirpation of the glands. There remains, then, a general resemblance between the symptoms of the two conditions, with differences, perhaps,

[1] British Medical Journal, September 21, 1901.
[2] C. R. Soc. de Biol., March 25, 1899.
[3] Arch. ital. de Biol., vol. xxx.

explicable from the differences in the duration and completeness of the parathyroid insufficiency. More light should be forthcoming from an anatomic and experimental study of exophthalmic goiter, and, indeed, Benjamins has recently examined the parathyroids in three cases of the disease, and has declared them to be practically normal. In several cases of exophthalmic goiter which have occurred in the Johns Hopkins Hospital, and in which portions—usually one whole lobe—of the thyroid have been removed for operation, I have been able, by the kind permission of Dr. Halsted, to search for the parathyroids. In this I have been assisted by Mr. Whipple, who will later publish a description of the histologic changes in these cases. It will suffice to say here briefly that in the tissues preserved from eight cases it has been possible to find parathyroid tissue in four. Since, however, the tissue in all of these cases had been handled a good deal, and many pieces removed for examination, it is quite possible that parathyroid tissue would have been found in all had the proper opportunity offered. In one other case, which died without operation, search at the autopsy failed to reveal any trace of parathyroid tissue. This was a case in which the symptoms were extraordinarily intense, and the patient actually died from the disease itself—a condition very different from that in the other cases in which the symptoms were moderate. In all of these cases it was difficult to find the parathyroids, and they were distinctly smaller than normal in all. In two of the cases no very definite change other than the decrease in size could be made out, while in the other two very distinct degenerative changes in the parenchyma cells, with overgrowth of connective tissue, could be observed. It seems justifiable, therefore, to conclude that there is evidence in these cases of distinct diminution in the bulk and degeneration and disappearance of the cells of these glands. Whether this indicates that the symptoms are those of parathyroid insufficiency is, however, another matter. Against this idea is the fact that recovery, or at least great amelioration of the symptoms, is so frequent after the operative extirpation of the one lobe of the thyroid, with which, as I have just shown, the parathyroids are probably always removed. If the disease were due to a parathyroid insufficiency it is hardly probable that the condition of the patient would be improved by removal of half of the bulk of the already insufficient parathyroids.

Nevertheless, in view of the anatomic changes in these glands and the favorable result obtained by Moussu, and in spite of the fact that favorable results have been reported in the treatment of this disease from the use of almost every possible remedy, parathyroid feeding has been instituted in one case in this hospital. For the past month this woman, whose symptoms are the usual ones in a moderate degree of development, has received daily twelve of the raw parathyroids of the cow. The glands used are the larger external ones, which lie embedded in the thymus and quite separate from the thyroid; twelve of such glands, therefore, represent approximately the parathyroid tissue of three cows. So far absolutely no effect has been noticed. The pulse-rate continues at about 120, tremors are marked, and the test-sheet of writing which she copies at intervals shows about the same shakiness. Still, if the parathyroid glands were less difficult to obtain, it seems desirable that further tests of this therapeutic measure should be made, and with this in view an extract of the gland is now being made. Similarly it seemed possible, from the observations of the epileptiform attacks seen in some of the dogs, that certain forms of epilepsy might be due to a similar cause. No opportunity has as yet offered itself, however, for the study of the glands in this disease, nor has it been possible to feed these patients with the parathyroid glands.

Probably other convulsive diseases might be suggested which could possibly be brought into relation with the alterations of this gland; at any rate, the aim of this incomplete paper will be largely attained if it succeeds in directing some attention to the study of so important and little known an organ.

PAROXYSMAL HEMATINURIA. (HÉMOGLOBINURIE A FRIGORE.)

By W. GILMAN THOMPSON, M.D.,
OF NEW YORK CITY.

The rarity and obscure nature of paroxysmal or intermittent hematinuria make the detailed report of the two following cases of interest:

Case I.—The patient is a lad, aged twenty years, of German parentage. He belongs to a neurotic family, his father being a very nervous man, and his mother indulging in hysteric paroxysms of anger in which she is said to lie upon the floor in violent jactitation, even frothing at the mouth and becoming unconscious. The patient in infancy was marasmic, but in childhood was in fair health up to his fourth year, when the first paroxysm of hemoglobinuria was observed, which has been followed by similar seizures during the past sixteen years. The first attack began during a sleigh-ride in which the boy's feet became chilled. Subsequent attacks have occurred, chiefly from September to May, on chilly days, but a few have arisen in midsummer from emotional causes. The patient's father stated to me that the boy "frequently goes outdoors on a very cold day without experiencing an attack, but any sudden fall of temperature will bring one on, and a raw wind has the same effect. Dry cold air is less apt to precipitate an attack than moist air; but even upon the coldest winter days, if the patient remain indoors, attacks are never experienced." The paroxysms are so uniform that a short description of one will serve not only for this case, but for others which have been reported: After brief exposure to moderate cold the hands and feet become stiff, numb, swollen, and cyanosed; there is a general sensation of chilliness, but a decided rigor is rare; there is an intense sensation of weariness, with yawning, severe headache, and abdominal cramps. Soon the face itches and burns, and large urticarial wheals appear upon the forehead, cheeks, and hands. The temperature rises two or three degrees, excessive thirst is experienced, and lumbar pain is complained of, chiefly over the region of the left kidney. Micturition becomes frequent, being desired every few minutes, but it is unaccompanied by pain or strangury. The first urine voided in the attack is of a dark red or port-wine color, and in all about a pint of blood-stained urine is passed during the entire paroxysm, which lasts about an hour, provided he can go promptly to bed and warm himself. The patient exceptionally has had two such attacks on the same day. At other times

he has had one seizure daily for a week or more, and again has passed a month or winter without a paroxysm. He complains of feeling weak and prostrated most of the time, and of being unable to apply himself to any work, mental or physical. He has tried to work as a telephone boy.

The patient was under observation in the Presbyterian Hospital four years ago in January, part of the time in the service of Andrew H. Smith; he was again treated at that institution after a short interval, and on August 20, 1901, he applied for treatment at the Eye Clinic of the Cornell Medical College Dispensary, where he was found by Robert G. Reese to have a double interstitial keratitis. During the past winter his case has been studied at my clinic at the Cornell Dispensary. He has, therefore, been under definite medical observation for more than four years. I have seen the patient in several typical attacks, such as that above described. He has never been jaundiced, and has found that diet and treatment with potassium iodid make little or no difference in his condition. In one attack he temporarily lost all muscular control of his legs and arms, and was so stiff as to be unable to rise from a chair. His feet and hands remained swollen, tender, bluish, and cold for three-quarters of an hour. Tactile sensation was diminished and retarded in the arms and legs. His temperature rose to 102° F. during the seizure, and next day became subnormal (97.4° F.). During six weeks that he spent in hospital his temperature rose several times to 100°, and as often fell to 97.6° F., showing considerable fluctuation between the paroxysms. While in hospital the boy was given potassium iodid up to two drachms per diem without benefit, as regarded his attacks, although he gained fifteen pounds in weight.

The patient's appearance strongly suggests congenital syphilis, and his expression is that of a degenerate. The bridge of the nose is broad and flat, the teeth are strikingly of the Hutchinson type, and the palatine arch is narrow and extremely deep; the arterial walls are thickened, and a pulmonic systolic bruit is heard; the superficial lymphatic glands are prominent. The boy's expression is dull and his manner listless. Physical examination of the lungs and abdominal viscera is negative; the heart, normal in size, is at times intermittent in action. Blood examination shows no anemia. When the boy was first in hospital, in 1899, the urine was repeatedly examined, and showed ordinary variations, from alkaline to acid, from 1014 to 1028 in specific gravity, and from 50 to 70 ounces in quantity. Phosphates were present in excess, and during the paroxysms albumin and hemoglobin were observed, but only at such times, as proved by repeated examinations On one occasion only were red blood corpuscles found in the urine, which were shrivelled and deformed. Two specimens examined for me by Dr. Hastings in connection with the dispensary clinic, which were passed during a paroxysm, gave a marked coagulum of albumin; acidity, normal; triple and amorphous phosphates in excess. Sugar, casts, and red blood corpuscles were absent. The first of these specimens, voided at the commencement of the attack, showed no hemoglobin, although, as stated, albumin was present; the second specimen gave oxyhemoglobin with the spectrum; a

third specimen, voided the following morning, presented neither hemoglobin nor albumin.

After an attack, and during the day following, the boy still showed evidence of prostration, having a sallow complexion and haggard face. He is mentally dull and physically weak between the paroxysms, so that he has been unable to undertake continuous employment. As his father expresses it, "his entire nervous system seems unstrung."

When I last saw the boy he had signs of an intermittent hydrarthrosis (hydrops articulorum intermittens), affecting the right knee, which at intervals of a few weeks becomes greatly swollen, and the integument over it becomes discolored. The condition is not painful, nor does it interfere with walking.

In this patient paroxysms have been induced by cold applied to the hands or feet, and in a few instances the only exciting cause was mental emotion.

Case II.—This patient was a native American boy, aged seventeen years, who was employed in a drug store. He was admitted to the Presbyterian Hospital, where, during part of his stay, he was in the service of F. P. Kinnicutt, through whose courtesy I am permitted for the first time to publish the case. The patient's family history was negative, except that his father was confined in an insane asylum, which, as in the previous case, adds confirmation to the fact that in many instances of hematinuria an hereditary history of neurosis, degeneracy, or other disorders of the nervous system is obtained. The boy's parents were said to be non-syphilitic, but as an infant he had "snuffles," and at two months of age a suspicious eruption upon the hands and soles of the feet, which was protracted for three weeks. His incisor teeth were very irregular, a condition which was attributed, however, to an early habit of continuously chewing upon bits of woollen cloth, as he was a very nervous child. When three years old the boy first had paroxysmal attacks, consisting of rigors, fever, jaundice, and the passage of dark colored urine. Constipation was present, and the stools were white. It was always noticed by the parents that the attacks were only induced by exposure to cold, or to a draught of air, and they lasted as long as the child was thus exposed; but the symptoms, excepting the jaundice, all disappeared within an hour after removal to a warm room. These attacks continued at intervals, and when the boy was five years old became serious, the urine being distinctly bloody and remaining dark colored for a day or two after an attack. It was also observed that whenever the fingers were placed in cold water they became purple, mottled, and numb. Subsequently the boy learned to remain indoors during cold weather, so that attacks were infrequent.

When at the age of thirteen years attacks similar to those above described were observed, with the addition of large urticarial swelling of the face and hands, the face became flushed, and the ears and nose were notably swollen Epigastric cramps were complained of, with frequent bilious vomiting. After the patient's last attack, before admission to the hospital, he was said to have

voided bloody urine for two weeks. During the summer the boy has always felt well, but in the winter he has been often ailing with malaise, constipation, and anorexia, although in the intervals between the attacks he has remained fairly comfortable. On admission to the hospital the patient was in the midst of a paroxysmal attack, and the feet were slightly edematous. Aside from slight enlargement of the spleen, which was palpable half an inch below the margin of the ribs, the viscera appeared normal. The urine contained blood pigment, a few red blood corpuscles, indican, a trace of albumin, and granular casts; the specific gravity was 1020; the temperature was 100.2° F., and the pulse 68. The blood pressure registered 112 mm. of mercury. The patient improved in a few hours, and subsequently an attack was experimentally induced by immersing the patient's hands for only two minutes in water at 60° F. A red line of demarcation formed upon the wrists at the level of immersion, and the hands became swollen, mottled, and purple. Upon application of friction to the hands, or after their immersion in warm water, the edema subsided. The patient remained under observation in the hospital for more than a month, during which time his weight rose from 106 to 114 pounds, and the albuminuria disappeared. He was treated simply with iron and laxatives.

These two cases are noteworthy for the early age (three and four years respectively) at which the symptoms began, for their long duration (fourteen and sixteen years), the prominence of urticaria, edema, and local cyanosis, and the probable existence of hereditary syphilis.

A diligent search of the literature of paroxysmal hemoglobinuria published during the past forty years reveals only 206 reported cases. Owing to the meager reports of many of the cases and the lack of blood examinations, and of accurate urinalysis in some of the earlier ones, it is impossible to give data in percentages of exact figures, but a sufficient number of observations remain to justify certain conclusions as to the etiology of this remarkable affection. Before proceeding to this discussion I shall briefly summarize the more important clinical features.

The geographical distribution of the disease is interesting. The great majority of the cases have been reported about equally from England, Germany, and France. A number have been reported also by Italian observers, and a few have been met with in Russia, Austria, Hungary, and Roumania. One or two cases have been reported from Scandinavia. In the warmer countries the disease naturally would be expected not to prevail, and with the exception of Italy

this appears to be the fact. Two genuine cases have, however, been observed in Smyrna by Diamantopulis, and one in Vera Cruz by Heinemann.[1] In the United States and Canada the disease is either extremely rare, or interest in it has been lacking, for very few cases have been reported, and most of them were among foreigners or those of immediate foreign descent, as in the two cases which I have been able to add to the list. This comparison is possibly due in part to the greater prevalence of hereditary syphilis among the poorer classes of northern European countries.

In females very few authentic cases have been met with, not more than 4 or 5 per cent. of the total number recorded.

The age at which the disease is most often first observed is in the third and fourth decades, but a few examples have been met with in earlier childhood, and one at the seventy-first year (Bruzelius[2]). One case was definitely known to first develop at the sixty-fourth year (Martienzo[3]), and Dr. Druitt's[4] case began in his fifty-first year. William Roberts[5] and Joseph[6] each saw a patient in the second year of age. One of my reported cases appeared in the third year, one in the fourth, and I have found reported one case each in the sixth and seventh year of age, two in the eighth, one in the eleventh, and one in the fourteenth.

The duration of the disease, on the average, is through a period of many years. A majority of cases have been known to exist from four to eight years. Dickinson[7] and Fagge[8] reported cases of eleven years' duration. The two cases reported in the first part of this article, which had persisted fourteen and sixteen years, respectively, are among the longest recorded.

The temperature usually rises during an attack to 102° or 103° F., reaching a maximum when the urine is most darkly colored. It both rises and falls abruptly. Some cases are afebrile, a few have a subnormal temperature, and in severe cases it has been much elevated, in two reaching 105° and 105.2° F., respectively (Heinemann,[1] Saundby[9]), in one 104° F. (Pye-Smith[10]), and in one 103.4° F. (Bristowe[11]).

The pulse is usually quickened, and sometimes becomes rapid and feeble or intermittent during the height of the attack. A *bruit de souffle* may be heard in the veins of the neck, but heart murmurs do not develop.

Respiration is unaffected, except as the rate may be slightly increased commensurately with the temperature.

Chills are of frequent occurrence. There may be one severe initial rigor or a succession of moderate chills, or the patient may feel cold throughout the attack. Of the twelve attacks observed in the same patient by Prior,[12] of Bonn, eight began with a decided chill. Sweating is often observed.

Pain is a prominent symptom in many cases. It is felt chiefly as a dull ache in the lumbar region, but may radiate forward over the abdomen or into the testicles or bladder. The legs and thighs are usually stiff, and either numb or painful during the height of the paroxysm. Abdominal pain is often colicky in character, as in the two cases above cited in detail.

The spleen has been found slightly enlarged in a few cases, and also the liver, and in a case of von Leube[13] both these organs appeared tender on pressure.

Jaundice is a common symptom, being noticed in about 15 per cent. of cases. It is of mild grade, appears rapidly with the paroxysm, and either subsides with it or outlasts it by two or three days. It is unaccompanied by biluria, and the stools are seldom of abnormal pallor. It is uncertain whether the jaundice is of hematogenous or hepatogenous origin, but most observers believe it to be of the latter type.

The urinalysis is distinctive and diagnostic. Albuminuria is an almost invariable accompaniment of the attacks, disappearing usually in the intervals. Both paraglobulin and serum albumin are observed in varying proportions. In Bristowe's[11] case the quantity of the latter was one-half that of globulin. Hyaline and granular casts may be present also. Several clinicians (Grandeau, Bault,[14] Saundby[9]) attest the occasional observation of paroxysmal attacks of albuminuria unaccompanied by hematinuria. The albuminuria in such cases may be accompanied by urticaria, cyanosis, and other symptoms of the more typical paroxysm, and is induced by similar causes—*i. e.*, fatigue or exposure to cold. In subsequent attacks the same patient may have hematinuria. Saundby[9] reports a case in which attacks of hematinuria with albuminuria alternated with attacks of albuminuria alone. The quantity of albumin is usually very small, often not exceeding 0.3 per cent (Bruzelius,[2] of Stock-

holm). The quantity of urine voided is somewhat subnormal during the paroxysm, but is usually above normal immediately thereafter and may amount to several quarts. During the paroxysm the frequency of micturition is increased, so that desire to empty the bladder may be experienced every half-hour. The time at which the urine is first found to contain blood pigment after the appearance of such primary symptoms as a chill, urticaria, extreme lassitude, etc., is from half an hour to three hours, the average being within an hour. The length of time during which the hematinuria remains varies from two or three to a dozen hours. Exceptionally it may persist until the following day. The color of the urine naturally varies with the quantity of blood pigment, from dark brown, or the color of port wine, to a chocolate brown, almost black. It is seldom modified by bile pigment, and the normal color is usually regained within a few hours of the subsidence of the paroxysm.

The total quantity of blood ingredients voided during a paroxysm is considerable. Salle[15] estimated the proportion of blood represented in the urine by pigment as equivalent to 12 parts of blood in 100 of urine. Others (Mesmet,[16] Hayem[17]) give a somewhat lower estimate—7 : 100. In a severe case the total quantity of bloody urine voided may reach two or three liters (seldom more). Red blood corpuscles are seldom found in the urine, and when present they are few in number and crenated, or otherwise deformed. I observed them in Case I. during one attack, but not in subsequent seizures. Bruzelius[2] reports a similar observation. Methemoglobin has been found in the urine in several cases, and biluria may be present. The specific gravity is usually somewhat high—1025 to 1027—for the percentage of urea is apt to be increased. In Roberts'[5] case it reached 5.2 per cent. and in Dickinson's[7] case 4.8 per cent. Oxalic acid is very often present in considerable excess, and a patient of Robin,[18] a young man, voided oxalic gravel.

Examination of the blood presents no constant diagnostic changes; in fact, many observers have failed to discover any change at all. Others report the finding of poikilocytes, colorless corpuscles, and granular, degenerated forms preceding a paroxysm. When attacks have been frequent and severe a moderate grade of secondary anemia is observed. Purpura has developed in several cases. From such observations it is argued that hemoglobinemia precedes the hemo-

globinuria. Hemophilia has not been observed in any case reported.

Other symptoms occasionally are observed during the paroxysm, such as nausea and vomiting, with a sensation of epigastric weight and oppression, and diarrhea.

In many cases there are decided evidences of perverted nutrition. A large proportion of the patients belong to neurotic families, and give evidence of various neuroses, especially vasomotor, such as urticaria and Raynaud's disease. A man seen by Hilton Fagge[8] lost the margins of both ears from symmetric gangrene and finally developed chronic nephritis, and Pye-Smith[10] reported two cases with gangrene of the ears and fingers or toes. In Druitt's[4] personal case Raynaud's symptoms were present, and Osler[19] reported a case complicated by Raynaud's disease and epileptic seizures.

Muscular effort is an exciting cause of the paroxysms in many instances, and in about 4 per cent. of the reported cases it has been the sole exciting cause. In a few more cases it has been an associated factor combined with exposure to cold. Walking is the special form of effort which usually precipitates an attack. In certain patients walking steadily for an hour or two, or for a distance of only two or three miles, invariably is followed by hemoglobinuria; in others it is not produced short of much more severe exertion, as that of a forced march. In a case reported by Bastianelli[20] the influence of cold was absolutely excluded; walking induced the paroxysms, but general gymnastic exercises continued for an hour failed to do so. Fleischer[21] reports a similar case, that of a soldier who had an attack whenever he walked continuously for an hour, but other forms of exercise were without effect. A third case, observed by H. Koster,[22] was entirely uninfluenced by cold, but forced marching induced attacks. This patient was a man, aged thirty-five years, who had contracted syphilis four years before. Five more cases have been reported (L. Dickinson,[7] Kast,[23] Robin[18]), one of them that of a woman, aged twenty-six years. In addition to these eight cases, in which walking was the exclusive cause of the paroxysms, a number have been observed in which they were induced occasionally by walking, and at other times by cold air or water. Thus Socor[24] met with an engineer, aged forty-five years, whose primary attack was due to cold and fatigue combined, but subsequently any exercise of the legs was a sufficient excitant. Another

patient, a young soldier, had a primary attack following exercise alone, but subsequent attacks were induced by cold (Bertelle[25]). Prior personally observed twelve paroxysms in the same patient, five of which were due to cold, one to exertion and a wetting, and the remaining three seizures were without assignable cause. Hilton Fagge[8] also reported two cases in which attacks appeared without discoverable cause in the warm months of June and August. F. Chvostek[26] advances the theory that those cases which are only induced by walking are akin to functional albuminuria, and are due to functional circulatory disturbance of the abdominal viscera induced by motion, combined with a diminished resistance of the red blood corpuscles.

The influence of cold alone, or of cold and wetting, predominates in the great majority of cases. The degree of cold and the duration of exposure to it which is necessary to produce a paroxysm varies in individuals and in the same persons at different times. A freezing temperature is by no means necessary, especially if the cold be applied to the hands or feet. As a rule, a temperature between that of freezing and 50° F. will induce an attack. In sensitive subjects very limited exposure of surface is sufficient, or very brief exposure of the entire body. Thus Ehrlich[27] was able to precipitate an attack in a woman by chilling for fifteen minutes one of her fingers which he had previously constricted with a rubber band. Flensburg[28] met with a child of eight years in whom he was able to precipitate an attack by constricting the arm and immersing it in snow for five minutes. Dr. Druitt's[4] first attack occurred while fishing in Scotland in a chilly wind, and the second four months later while skating without an overcoat, but subsequently attacks followed five minutes' standing in a draughty railway station, and a brief drive in a hansom cab against the wind. One or two patients have been so sensitive to attacks that they were unable ever to go outdoors without having one. A common cause of the primary attack is that of falling into cold water, or becoming drenched in a cold rain. In almost all the typical cases attacks can be induced at will by immersing either the hands or feet for ten or twenty minutes in water at a temperature of about 50° F. This is observed even in summer, as in a patient of Rosenbach[29] and Ehrlich.[27] One of Sir William Roberts'[5] patients was as liable to attacks in summer as in winter, and Bruzelius[2] reports the case of a

woman who could reproduce attacks by merely laying the hands for a few moments upon a cold surface, such as marble.

Information from autopsies is lacking, for the paroxysms are never fatal, and patients who die from intercurrent diseases are not likely to do so during a paroxysm, which, from the nature of the case, is brought on chiefly by voluntary exposure to cold or fatigue while in a condition of comparative health. A patient of Prior,[12] of Bonn, developed paroxysmal hematinuria in his thirty-eighth year. Five years later he died of general tuberculosis, but the kidneys were found entirely normal. In Demme's[30] case postmortem examination revealed slight enlargement and marked congestion of both liver and spleen, and ecchymoses in the submucosa of the intestine. The kidney tubules were filled with detritus of disorganized red blood corpuscles, but the kidneys were unaltered in structure. Brunelle[31] lost a patient from tuberculosis who had had typical paroxysms induced by slight exposure to cold in winter. The liver was congested; the blood was normal; the kidneys showed a few slender bundles of connective tissue and slight dilatation of the tubules, but their epithelium was normal. Germoing[32] lost a patient, aged sixty years, who had had paroxysmal attacks of hemoglobinuria for three years. The kidneys were found normal excepting slight pigmentation of the tubular epithelium, and a slight degree of coagulation necrosis of some of the epithelial cells.

The only disease with which the condition under discussion is associated with a frequency which justifies the assumption of a causative relationship is syphilis. Of six cases reported by Copeman,[33] all were syphilitic, and in approximately one-third of all cases a syphilitic taint, either hereditary or acquired, has been noticeable. Still other cases, in which syphilis has been a suspected factor, have been benefited or cured by antisyphilitic treatment.

The theory of the nature of paroxysmal hematinuria has given rise to much discussion, and the difficulty of formulating a theory of general application is manifest from the number and variety of hypotheses set forth, which are almost as numerous as the reported cases. Thus it has been suggested that the malady originates (1) in the kidneys; (2) the blood in general; (3) the capillaries; (4) the liver; (5) the spleen, in each case arising through nervous shock of external cold; that it is (6) a blood dyscrasia in which there is a congenital or acquired instability of the red blood corpuscles; that (7) the corpuscles are

normal, but there is a fundamental vasomotor neurosis; that (8) the primary shock is not thermic, but mechanic; that (9) there is a special toxemia in operation; that (10) there is a special neurosis producing the attacks.

That the kidneys are primarily at fault is the earliest theory of the origin of hemoglobinuria, as first argued by Harley[34] and Sir William Gull,[35] and later by Hayem[17] and Robin.[18] Harley wrote of an "intense congestion of the chylopoietic viscera of transient and periodic character." The chief experimental support of this theory was offered by Lichtheim,[36] who inserted canulæ into the ureters of a dog, through which he injected sterilized water on the one side, and ammoniacal urine on the other. The urine subsequently secreted contained blood pigment from that side only upon which the ammoniacal urine had been injected, that coming from the other side being normal. Roberts[5] also argued in favor of an intense sudden renal congestion with local dilatation of capillaries and consequent stagnation of the renal blood. Stephen Mackenzie[37] argued that an intense renal congestion forced the blood under pressure into the glomeruli, where hemoglobin was liberated.

I am disposed to disregard the renal theory upon the following grounds: (1) there is no positive evidence that the kidneys are any more congested than other abdominal viscera, such as the liver and spleen; (2) there is no postmortem evidence of any distinctive renal changes; (3) the slight degree of exposure to cold which suffices to induce the paroxysms in many cases cannot reasonably be believed to influence the kidneys; (4) in many cases fatigue or emotional excitement may induce paroxysms irrespective of cold, and finally certain phenomena of the paroxysms, such as the urticaria, cyanosis, and especially the elevation of body temperature, cannot be accounted for upon the basis of a local renal influence, especially as they sometimes, like the albuminuria, are observed without accompanying hematuria.

The uric and oxalic acid theory of Haig,[38] which has been supported also by Foulerton and von Rossem,[39] is discountenanced by the fact that these acids are not demonstrable in excess in any considerable number of cases, nor is it probable that they could be produced in quantity in the very short time (a few minutes only) intervening between the moment of exposure of the patient and the onset of symptoms of the paroxysm. There is, moreover, no evidence that

the disease especially affects the gouty, or those suffering from the uric acid diathesis or oxaluria.

The theory of Brunelle[31] and others that congestion of the liver results in excessive destruction of red corpuscles cannot be regarded as the sole cause of the hemoglobinuria, for the same reasons as those above given in regard to the influence of the kidneys. Ralfe[40] holds that when only a few red corpuscles are destroyed the globulin is excreted as albumin and the pigment is cared for by the liver and spleen; destruction of a large number of corpuscles in the liver, however, permits the hemoglobin to be excreted by the kidneys. Ponfick, and subsequently Litten,[41] have argued that the blood may contain an excess of free hemoglobin without its excretion in the urine; that the liver disposes of ordinary quantities of hemoglobin as it does of sugar, but, as in the case of glycosuria, hemoglobinuria may result when the normal hepatic functions are overtaxed.

It has been argued that the disorder originates in the blood itself (Fagge[8]). As against this hypothesis, it is impossible that any considerable chilling of the entire blood in the body can follow such slight exposure to cold as, for example, that of cooling one finger or laying the hand upon a cool surface. This hypothesis, moreover, fails to explain the attacks induced by fatigue or purely neurotic influences. Of more importance is the theory of a special blood dyscrasia, consisting of a weakness of the red corpuscles (Copeman[33]), or a developmental fault (Hénocque[42]), either congenital or acquired, whereby the red corpuscles are readily disassociated by ordinarily trivial causes, such as capillary dilatation and stagnation of the blood, with accumulation of carbonic acid. H. Chvostek[26] favors this view, while denying that cold *per se* affects the blood. His theory is that the feeble corpuscles are disorganized mechanically. Through the influence of cold or vascular changes resulting from fatigue, capillary stasis ensues, either in peripheral vessels or the viscera, and such stasis results in hemoglobinemia. Through abnormally increased innervation of the peripheral vessels, and consequent rise of blood pressure in the viscera, hemoglobinuria follows. In support of this theory Chvostek cites experiments with amyl nitrite, in which, by dilatation of the peripheral vessels, hemoglobinuria was controlled.

The argument that paroxysmal hemoglobinuria is due to a condition of constitutional degeneracy, inherited or acquired, is open to but few

exceptions. A large proportion of patients are syphilitic, but by no means all are. A number more belong to families in which there has been ancestral degeneracy in the form of insanity or exaggerated neurotic tendencies. In still other patients no such condition or history can be traced, or the disease may first develop so late in life as to preclude the probability of inherited or congenital dyscrasiæ which have never given earlier manifestations. For example: Bamberger[43] cites the case of a coachman, aged forty-nine years, who was in robust health up to his forty-seventh year, when the hemoglobinuria attacks first began. The attacks could be induced by immersing the feet in cold water for five minutes. They were accompanied by contraction of the pupils, which also became insensible to light. Pye-Smith[10] reported a case developing for the first time in a man aged sixty years. James Tyson[44] and Allen J. Smith suggest the possibility of participation of the adrenals and their associated sympathetic ganglia in the hemoglobinuric process.

In concluding this discussion of the etiology of paroxysmal hemoglobinuria it seems that no theory is satisfactory which does not attribute the chief influence to the nervous system. The number, variety, suddenness, and transitory nature of the symptoms cannot be otherwise satisfactorily explained. The chills, the temperature, the cyanosis, the urticaria, the pain and other sensory disturbances, and the variations of the pulse are all nervous phenomena, of equal prominence and importance with the hemoglobinuria. The latter is, in fact, merely incident to the attack, not its sole important feature, and, as has been stated above, it may be absent from an otherwise entirely typical paroxysm. Further confirmation of this view is found in the fact that so large a proportion of the patients are either themselves degenerate or neurotic, or possess such inheritance. With such profound vasomotor neuroses as give superficial evidence, it is easy to conceive that the deep-seated viscera, such as the liver and spleen, may have their functions temporarily disturbed, with the resulting production of hemoglobinemia, from which is a simple step to hemoglobinuria. I would submit, therefore, that paroxysmal hemoglobinuria may be defined as *a profound neurosis, chiefly affecting the vasomotor system, and called into activity by exposure to moderate degrees of cold, by muscular fatigue, or mental emotion.*

The features of difference between malarial hemoglobinuria and the

paroxysmal type are distinct. With the former the incidence of the disease in the tropics, its periodicity, its relation to quinine, the frequent presence of the plasmodium malariæ and of typical cachexia, and the longer duration and fatality of the attacks are characteristic. Malarial hemoglobinuria usually presents prodromal symptoms, lasting through a period of hours or days, such as fever, malaise, anorexia, and lumbar pains. Vomiting is more common, chill more intense; diarrhea is severe, and anuria and nephritis may develop. Besides these features, in malaria there is an absence of the special angioneurotic symptoms that characterize the paroxysmal form, such as urticaria, local cyanosis, and modifications in arterial tension. In the paroxysmal form the type of patient, often more or less degenerate, is different, and so are the influence of cold and the methods and results of treatment; in fact, the presence of hematin or hemoglobin in the urine is the only symptom which the two disorders uniformly present in common.

Other types of hemoglobinuria are readily distinguished from the paroxysmal form by their different etiology and behavior; such are the hemoglobinurias following extensive burns, the ingestion of chemical poisons, such as potassium chlorate, turpentine, carbolic acid, phosphorus, the mineral acids; organic poisons, such as that of the mushroom (*Morchella esculenta*), and traumatic cases, such as have lately been reported by Saunders, Filatow, and others. In all these forms of hemoglobinuria the distinctive paroxysmal type is lacking, with its features of fever and angioneurotic symptoms, and the etiology is plainly found in a direct destructive action upon the red corpuscles without associated vasomotor phenomena.

It is interesting to note that horses may have hemoglobinuria when after a long period of stabling with high feeding they are taken out and driven hard or exposed to cold. Professor James Law, in describing this condition in the *Special Report on Diseases of the Horse* (published in 1890 by the Bureau of Animal Industry of the United States Department of Agriculture), calls attention to a special anatomical condition of the liver which exists only in solipeds, whereby the vascular contents of the liver and portal veins may be aspirated directly into the general circulation through certain large branches of the portal system. Von Babes has described an infectious form of hemoglobinuria occurring in Roumanian cattle.

The treatment of paroxysmal hemoglobinuria is mainly satisfactory in the markedly syphilitic cases, several of which have been reported as cured by the use of mercury and potassium iodide (Fagge,[8] Ehrlich,[27] Mackenzie[37]). Removal to a warm climate during the winter months is completely preventive, as it was in the case of Dr. Druitt, who remained free from attacks while residing in India. Patients who are unable to emigrate in winter can prevent attacks at home, to a great extent, by avoiding sources of mental and bodily fatigue and by being warmly clad on cold or chilly days. The wearing of heavy woollen under-garments and fur-lined gloves and shoes will do much to ward off attacks. The seizures are most likely to take place in the early morning hours, and a chilly, damp atmosphere is worse than clear, dry cold.

The use of stimulants should be prohibited, for the depression which follows may render the patient more susceptible to the influence of cold. Medicines in general, aside from antisyphilitic treatment, are of little value for this affection, but Saundby recommends the use of calcium chlorid as a hemostatic, not above gr. vj, to be taken within two hours. H. Chvostek[26] believes that amyl nitrite inhalations may abort an attack, and the use of arsenic is recommended by several clinicians. Tyson suggests the administration of suprarenal extract, but thyroid extract might prove more beneficial, as it possesses such remarkable effect over many functional and nutritional disorders, and, unlike the suprarenal extract, it does not raise arterial tension—a condition which Chvostek and many others have claimed is a causative factor in hemoglobinuria.

Attacks may be aborted by a hot bath or by going to bed with hot-water bottles and blankets, and by taking a simple hot draught or cup of hot broth or milk. Diffusible stimulants are useful, such as chloroform-water, Hoffmann's anodyne, or aromatic spirit of ammonia.

Historical Note.—The first distinct case of intermittent or paroxysmal hemoglobinuria recorded in literature is one reported by Charles Stewart in Duncan's *Medical Commentaries* for 1794, but this appears to have been of malarial origin. In the first half of the nineteenth century three or four similar cases were recorded by Gergères (1838), Rayer (1841), and Defer (1849). Owing to the imperfections of urinalysis, and absence of blood examinations at this

early period, it is doubtful whether these cases represented hematuria or hemoglobinuria. In 1854 Dressler reported a case of what he termed "intermittent chromaturie" with albuminuria in which he noted the absence of red corpuscles in the urine on microscopic search. George Harley[34] in 1865 recorded two cases of what he designated "intermittent hemoglobinuria," in which he ascribed the condition to pigment derived from the red blood corpuscles, and by means of engravings represented pigmented casts and granular pigment derived from hemoglobin in the urine. The following year (1866) Sir William Gull[35] first observed hematin crystals in the urine. The spectroscopic demonstration of the urinary hemoglobin appears to have been made first by G. Scheidlin[45] in 1872. Since that date a few cases of intermittent or paroxysmal, non-malarial hemoglobinuria have been reported almost every year, and up to 1879 William Roberts, writing in Reynolds' *System of Medicine*, was able to collect twenty authentic cases published in England. In 1894 F. Chvostek,[26] assistant to Professor Neusser's clinic, published an elaborate monograph of more than one hundred pages, entitled *Ueber das Wesen der Paroxysmalen Haemoglobinurie*, in which he advanced some original ideas as to etiology. Since that date numerous isolated cases have been reported up to the present time.

Bibliography.

1. Heinemann. Virch. Arch., Bd. 102.
2. Bruzelius. Hygeia (Stockholm), December, 1888. Zeit. f. klin. Med., vol. xi. p. 459.
3. Martienzo. Lancet, August 18, 1899.
4. Druitt. Medical Times and Gazette, 1873, 1879, p. 215.
5. Roberts. Reynolds' System of Medicine, vol. v., 1879.
6. Joseph. Berlin. klin. Wochenschr., July 1, 1890. Medical Press and Circular, July 22, 1890.
7. Dickinson. Med. Chirurg. Trans., 1865, p. 175.
8. Fagge. Practice of Medicine, vol. ii.
9. Saundby. Medical Times, May 1, 1880.
10. Pye-Smith. Fagge's Practice of Medicine, vol. ii.
11. Bristowe. British Medical Journal, May 4, 1890.
12. Prior. Münch. med. Woch., Nos. 30–33, 1888.
13. Von Leube. Sitzungsber. d. Würzburg. phys. med. Gesellschaft, 1886.
14. Bault. Charcot's Traité de Méd., tome v. p. 616.
15. Salle. Bull. de la soc. des méd. et nat. de Jassy (Roumania), June, 1889.
16. Mesnet. Arch. gén. de méd., May, 1881.
17. Hayem. La Sem. Méd., July 18, 1889. Du Sang, etc., Paris, 1889. Gaz. Hebdom., 1889, No. 11.
18. Robin. La Sem. Méd., April 18, 1889. Wien. med. Bl., 1888, No. 38. Gaz. de Paris, 1888, No. 14.
19. Osler. Practice of Medicine, p. 853, 1901.
20. Bastianelli. Le Bull. Méd., July 21, 1890. Centralblatt für klin. Med., p. 148, 1889.

21. Fleischer. Berlin. klin. Woch., No. 1881, 47.
22. Koster. Therap. Monatsheft., February, 1894.
23. Kast. Münch. med. Woch., May 19, 1892. Deut. med. Woch., 1884, No. 52.
24. Socor. Bull. de la soc. des méd. et nat. de Jassy (Roumania), June, 1889.
25. Bertelle. Arch. de méd. et pharmacie militaires, February, 1891.
26. Chvostek. Ueber das Wesen der Paroxysmalen Haemoglobinurie, 1895.
27. Ehrlich. Deut. med. Woch., 1881. Charité Annalen, vol. x. p. 142, 1885. Zeit. f. Klin. Med., vol. iii. p. 383, 1881.
28. Flensburg. Rev. Internat. de Bibliog., Beyreuth, January 25, 1894.
29. Rosenbach. Berlin. klin. Woch., No. 10, p. 132, 1880.
30. Demme. Virchow's Jahresb., vol. ii. p. 687, 1886.
31. Brunelle. Le Bull. Méd., June 10, 1890. Bull. Méd. du Nord., September, 1890.
32. Germoing. Medical Press and Circular, August 29, 1889.
33. Copeman. British Medical Journal, May 4, 1890. Lancet, August 10 and 17, 1890; October 11, 1891.
34. Harley. Med. Chir. Transactions, vol. lxviii. p. 161, 1865.
35. Gull. Guy's Hospital Reports, 3 ser., vol. xii. p. 381, 1866.
36. Lichtheim. Sammlung. klin. Vorträge, 1878, No. 134.
37. Mackenzie. Lancet, vol. ii. p. 725, 1879.
38. Haig. Transactions Medical Society of London, 1892.
39. Von Rossem. Lancet, October 4, 1891. Centralblatt f. med. Wissenschaft., 1878, p. 488.
40. Ralfe. Lancet, 1883, No. 17.
41. Litten. Deut. med. Woch., 1883, No. 50. Zeit. f. klin. Med., vol. iii. p. 385.
42. Hénocque. Dict. encyc. des sci. méd.
43. Bamberger. Deut. med. Zeit., 1888. Alg. Wien. med. Zeit., 1884, No. 45.
44. Tyson. Practice of Medicine, p. 692.
45. Scheidlin. Berlin. klin. Woch., 1872, p. 237.

REPORT OF A CASE OF PULSATING EMPYEMA NECESSITATIS, WITH THREE STRONGLY PULSATING TUMORS.

By FREDERICK P. HENRY, M.D.,
OF PHILADELPHIA.

In Volume III. of the *Transactions of the Philadelphia County Medical Society*, 1881, page 85, in the course of the discussion of a paper by the late Dr. Edward T. Bruen, entitled "Clinical Notes Relative to Physical Diagnosis," I reported, in abstract, a case of pulsating empyema necessitatis that had been recently under my care at the Episcopal Hospital. As "discussions" are not recorded in the *Index Medicus*, or anywhere else, the case to which I refer is practically inaccessible to all students of the rare disease in question. It has, however, been quoted by two writers upon pulsating empyema: by Osler in Volume III. and by Wilson in Volume VIII. of the Transactions of the Association of American Physicians. In the latter it appears as No. 38 among the cases collected by Wilson and Eshner from the literature of the disease. On referring to my remarks upon Dr. Bruen's paper above mentioned I find the statement that "further details are now withheld, as the notes of the case will probably soon be published in full." Twenty-two years have elapsed since this statement was made, and the promise which it implies has not yet been fulfilled. The reason for this delay was apparently good and sufficient, viz., the absence of complete notes of the case. It is evident that such notes were once in existence, for in the scanty record of the case that I have preserved I find the following: "April 16. Woman more comfortable; cough diminished. For details of physical examination, see ward notes."

At the Episcopal Hospital the only existing records of this remarkable case are her name, Elizabeth M., the diagnosis, pulsating

empyema, and the admission number, 295. The ward notes above mentioned, which one is requested, with exasperating irony, to "see," have completely disappeared. Fortunately, I have notes of the main facts of the case, and I believe they are sufficient to warrant its publication.

The patient was a woman, aged about thirty years, who was admitted to the Episcopal Hospital on April 14, 1880. On the left side of her chest there were three strongly pulsating tumors: one in the mammary region, of about the size of half a large orange; a second, much smaller and of conical shape, in the left anterolateral region—*i. e.*, in the eighth intercostal space, in a line with the anterior axillary border—and a third, the largest of the three, in the left posteroinferior region, its long diameter—about four inches—corresponding with that of the vertebral column. All three of these tumors possessed a strong, systolic, expansile pulsation. On palpating the large anterior tumor, the one in the left mammary region, splashing sounds were produced, and a sensation was communicated to the fingers precisely like that experienced on handling a large hernial protrusion. It was evident that the tumor contained both air and fluid. There was dulness on percussion posteriorly up to the middle of the scapula. The line of dulness curved downward and forward until, in front, the whole of the anterior surface of the left thorax, usually occupied by the normal lung, was resonant almost to the point of tympany, while over the larger anterior tumor it was decidedly tympanitic. The semilunar tympanitic area of Traube was replaced by flatness on percussion. It was estimated that the depth of the fluid in front was about two inches, and that the rest of the pleural cavity anteriorly was occupied by air. This may seem to contradict the statement that air and fluid were both present in the pulsating tumor in the mammary region, and to imply that the pulsation was due to an impact derived from the heart upon the air which it contained. I can only reply that the tumor undoubtedly contained both air and fluid, that it was tympanitic on percussion, and that it pulsated at least as strongly as the two other tumors, which contained pus alone. Behind, above the line of dulness, there was unusually deep-pitched resonance and decided amphoric breathing. This amphoric quality of the respiration could, in fact, be heard all over the chest except over the posterior tumor, its greatest intensity being over the upper half of the scapula and between the upper half of the posterior border of the scapula and the vertebral column. There are no notes concerning the presence or absence of vocal fremitus, metallic tinkling, coin sound, or succussion splash.

From the meager history of the case it appears that the woman was in good health up to the time of the attack (date not stated), which began with pain in the side, and not with the explosive symptoms which so often attend the rupture of lung tissue. In other

words, the empyema probably began as such or was secondary to pneumonia or other infection, and was not the consequence of rupture of the lung from tubercle, abscess, gangrene, or other cause. Another fact corroborating the view that the perforation of lung or bronchus was the consequence and not the cause of the empyema was the patient's recollection of a night during which she had coughed and expectorated almost incessantly. It was probably at that time that the pneumothorax was established. Whether or not the tumors on the chest wall were present before that event could not be ascertained, but it is practically certain that they were.

The question of the date of the pulsation is a most interesting one. The sequence of events was probably as follows: The case began as empyema. The pus then pointed in the three above-mentioned spots upon the chest wall—empyema necessitatis. Before the pus could discharge itself through the integument a bronchus was perforated and air admitted into the pleural sac. Now the question arises whether the tumors were pulsating before the establishment of pneumothorax or whether the pulsation was synchronous with and dependent upon the latter. I am in favor of the latter supposition: First, because if the pulsation had preceded the rupture into the bronchus it would probably have ceased on the occurrence of that event and the synchronous discharge of pus. This view is warranted by the fact that in most, if not in all, cases of pulsating empyema the pulsation has ceased on the withdrawal of a moderate quantity of pus by aspiration. Secondly, the presence of air in the pleural sac is a contributory cause of pulsation, although it may not be, as Féréol supposed, indispensable to it.

In cases of pulsating empyema with pneumothorax the air is usually, if not always, under high tension. What was the condition of the air, as regards tension, in my case it is impossible to say, and it is impossible to determine the tension of the air in any case of pneumothorax without the aid of manometric experiments, which are, practically, never employed in clinical medicine. We must regard the question of the exact tension of the air in any given case of pneumothorax as *practically*[1] insoluble. The next question to arise is whether we can, by means of the physical signs, determine a pneumothorax to be "closed" or "open." I know of no certain

[1] I emphasize the word "practically," for, theoretically, there is no difficulty about it.

method of doing so. Even amphoric, metallic breathing, the most reliable sign of communication between pleural sac and bronchi, is heard in cases of closed pneumothorax. There is, however, one experiment which, if successful, settles the question in favor of open pneumothorax, but which, if unsuccessful, does not necessarily determine that it is closed. The patient is made to lie on the affected side, which is still further compressed by the hands of the examiner. He is then made to sit up or to turn to the other side, while at the same time the pressure of the hands is relaxed. By this means, if the case is one of open pneumothorax, air may be drawn into the pleural sac and give rise to gurgling and metallic sounds as the bubbles rise in the fluid and break upon its surface.

To return to my case:

On the day after admission—*i. e.*, on April 15, 1880—paracentesis was performed by the late Professor John Ashhurst, Jr., the site of the puncture being the small conical tumor in the eighth interspace. More than a quart of thick, offensive pus was withdrawn, when, some air escaping, it was thought advisable to desist. The pus was so thick that it could scarcely be poured from the bottle into which it was aspirated, and was compared by one present to an infant's feces. By the time a quart was removed the pulsation in the large anterior tumor—the one in the left mammary region—had ceased, and also the gurgling on palpation. The posterior tumor was greatly diminished in tension, but the patient being still under the influence of ether at the time I left the hospital, I did not ascertain whether the pulsation in it had also ceased. The position of the heart remained unchanged. Coughing still produced a decided bulging of the large anterior tumor, although much less than before the operation. This bulging was doubtless produced by air alone.

April 22, 1880. This morning the patient was found bathed in pus, which was so fetid as to cause one of the nurses to faint, after which she vomited, complained of headache, and was laid up for twenty-four hours. The plaster had become loosened and the puncture made by the trocar had enlarged. Through the opening I introduced a flexible catheter, and injected about a pint of carbolic acid solution, 1 : 60. The side was then enveloped in oakum.

23*d*. Passed in the catheter for about six inches in a direction closely applied to the left thoracic wall and injected a somewhat larger quantity of the same solution. I ceased on the patient's beginning to cough and removed the catheter. The act of coughing caused the injected fluid to spurt out for a distance of two or three feet. Some pus, about two ounces, escaped with the last portion of the carbolic acid solution.

27*th*. A No. 11 catheter could be introduced but a very short distance,

and then could be felt through the parietes of the chest and appeared to be bent on itself. After the injection of a few ounces of carbolic acid solution—one drachm to the quart—the patient began to cough, and the injection was stopped. Coughing brought away a few ounces of pus, which spurted from the opening.

Nothing further is known concerning this case beyond the facts that a drainage tube was subsequently inserted by Dr. Ashhurst at my request, and that the woman was removed from the hospital and was alive a year afterward.

The case is almost unique as regards the number of pulsating tumors, there being but one other, that of Chvostek (Case XXIII., in Wilson's series), in which there were three.

There has been much discussion concerning the cause of pulsation in certain rare cases of pleurisy, and it is manifest that no single cause or set of causes is always operative. According to Féréol, the presence of air in the pleural sac is indispensable to the production of pulsating pleurisy. He states that it is often latent, which simply means that it is difficult of detection. This necessarily follows from the fact that the effusion is generally large, the air being forced backward to the root of the lung, laterally to the neighborhood of the pericardium, or elsewhere. Although the air may be small in amount, its anomalous situation may render it easy of detection, as in the case I report, in which it was contained in one of the pulsating tumors. The air must also be under considerable tension from the pressure of the surrounding fluid, and shut off from free communication with the bronchi. Under these circumstances it forms an elastic cushion, which transmits the pulsations of the heart to the effusion and through the latter to the chest wall.

On the other hand, Roux considers the presence of pneumothorax as unfavorable to the production of pulsation, because the air, being compressible, would yield to and diminish the force of the cardiac pulsations. There can be no doubt that Féréol's theory is not tenable, for, though the coexistence of pneumothorax may be the rule in cases of pulsating pleurisy, there are undoubted exceptions to it.

In quite a number of cases the pulsations of the heart have been transmitted through the lung, which was compressed into a solid mass and adherent to the pericardium.

In two cases reported by Traube there was coexisting pericardial effusion, with the heart displaced to the right. He explains the pul-

sation by the greater degree of mobility possessed by the heart on account of the surrounding effusion, but attributes a large share of the phenomenon to the relaxation of the chest wall occasioned by destruction of the thoracic pleura.

Lépine is of the opinion that pulsating pleurisy (endopulsation) may be more common than is generally supposed. In his case it was discovered, so to speak, accidentally, and was of limited area. He thinks it reasonable, therefore, to suppose that careful palpation of various parts of the chest wall, and especially over the attachments of the diaphragm, might lead to its discovery in cases in which, but for such examination, it would be entirely overlooked. According to Lépine, the conditions giving rise to pulsation are the following: Complete compression of the lung by the pressure of the effusion, rigidity of the mediastinum, and a certain degree of tension of the diaphragm. If the lung is not compressed it will yield to the blows of the heart and extinguish them; if the mediastinal partition yields to the blows of the heart they will be "*absorbed*" by the sound lung. Finally, the diaphragm must be immovable, so far as the respiratory act is concerned, and yet capable of transmitting the cardiac impulse to the surface—*i. e.*, it must be in a certain state of tension impossible to define with precision.

After a careful study of many of the reported cases it appears to the writer that the most important factors in the production of pulsating pleurisy are (1) left-sided and large effusion, (2) relaxation of the thoracic wall from paresis of the intercostal muscles, and (3) a somewhat forcible heart beat. The presence of air in the pleural sac under great tension and the adhesion of the compressed lung to the pericardium are co-operating but not essential causes.

It is customary for writers on pulsating pleurisy to group under the same head cases of intrapleural pulsation (endopulsation, as it is called by Lépine) and those with a pulsating tumor. So far as I know, Dr. Samuel West[1] is the only writer who has drawn a distinction between the general systolic shock of intrapleural pulsation and the expansile extrapleural pulsation observed in pulsating empyema necessitatis. To the writer it seems that this distinction is not sufficiently recognized, and also that it is unscientific to include these two varieties of pulsation in the same category. It may be, it

[1] Med. Chirurg. Trans., vol. lxxx. p. 239.

is true, that an intrapleural pulsation may become extrapleural by the pointing of the pus, as in the cases of Lorenzutti and Roux. On the other hand, however, an intrapleural pulsation may occur in cases of serous effusion, whereas an extrapleural pulsating pleurisy is, of necessity, purulent, so that the term empyema necessitatis is applicable to it in more senses than one.

The rarity of pulsating pleurisy, whether the pulsation be intrapleural or extrapleural, is shown by the fact that Alfred Keppler,[1] after searching the literature of more than two hundred years (from 1640 to 1887), was able to collect only thirty-eight examples of it. In 1893 J. C. Wilson tabulated sixty-eight cases of this rare disease, two of which had been recently under his own observation. I append brief abstracts of fifteen additional cases, all of which except two, the case of Bimmerman [1889] and Florand [1885], were published at a later date than Wilson's valuable contribution. Comby, who published a monograph on pulsating empyema in 1895, and who was evidently unacquainted with Wilson's paper, was able to collect but forty-seven cases of the disease. These, however, are reported at length. In this connection I may call attention to a mistake that has been made by both Keppler and Wilson. Wilson's Case II. is taken from Keppler's series and is wrongly ascribed to Pelletan. The case in question is to be found in Bérard's *Traité du diagnostic dans les maladies chirurgicales*, Paris, 1837, p. 179, and is entitled "Empyème pris pour un anévrisme." There can be no doubt about the identity of the case in question, for both Keppler and Wilson mention the circumstance that a probe introduced by a student into the opening which had been made in the pulsating tumor slipped from his grasp into the pleural cavity, from which it was subsequently removed by incision. This interesting circumstance is also related by Bérard. Comby, in his series, rightly assigns the case to Bérard.

The following cases of pulsating pleurisy added to the sixty-eight in Wilson's table increase the number by fifteen, making eighty-three in all.

Case I., Lorenzutti (*Annali Universali di medicina e chirurgia*, 1875, vol. ccxxxii. p. 385).—In this case there was first observed a general intrapleural pulsation over the lower two-thirds of the left thorax. A day or two

[1] Deutsches Archiv f. klin. Med., 1887, Bd. xli., p. 220.

later a tumor with expansile pulsation appeared over the left nipple. Aspiration. Cessation of pulsation when 600 grams of pus were removed. In all, three kilograms were withdrawn. Later, drainage tube inserted. Death a few days thereafter. Autopsy.

Case II., Proust (*Journal de médecine de Paris*, 1885, vol. ix. p. 25).—Woman, aged twenty-three years. Left-sided empyema with intrapleural pulsation. No pneumothorax demonstrable.

Case III., Florand (*La France médicale*, 1886, i. p. 158).—Woman, aged twenty-seven years. The disease began as an ordinary pleurisy, with serous effusion. Thoracentesis on January 27th, when two liters of serous effusion were withdrawn. Pulsation detected on March 24th. Second tapping on March 27th, when a liter and a half of pus was removed. Third tapping on April 18th; 1800 grams of pus. Pleurotomy on May 1st, followed by washing out pleural sac with solutions of boric acid and zinc chloride. Patient entirely well by end of November, with marked retraction of chest on left side.

Case IV., Bimmerman (*Geneeskundig Tijdschrift voor Nederlandsch Indië*, 1889, xxviii.).—Boy, aged nine years. Empyema pulsans (intrapleural). Liter of pus removed. Pleural sac washed out with 2 per cent. boric acid solution. Cessation of pulsation after removal of pus. Result of case not stated. Very brief article.

Case V., Pittarelli (*Gazz. degli ospedali*, 1893, xiv. p. 1260).—Male, aged thirty years. Left-sided effusion. Pulsation (intrapleural) over lower two-thirds of left side. Pus obtained by exploratory puncture. Several aspirations. Cure by author's method of injecting solutions of "soda" (3 : 1000) and sublimate (1 : 9000) coincidently with the withdrawal of the pus.

Case VI., Béclère (*Bulletins et mémoires de la Soc. méd. des hôpitaux de Paris*, 1894, xi. p. 339).—Case I. Male, aged thirty-one years. Left-sided, intrapleural pulsation. Disease began with cough in August, 1891. Previous health excellent. In November succussion sound heard by patient and compared by him to the noise of a barrel half full of water. Seen by Dujardin-Beaumetz in May, 1892, who made the diagnosis of pyopneumothorax. Seen by Béclère on May 8, 1893. Extended left-sided intrapleural pulsation; no tumor, no demonstrable pneumothorax, although succussion felt by patient two or three weeks before. Twenty-eight hundred grams of pus withdrawn by aspiration. Patient exhibited three years later in excellent health. (See *Bulletins et mémoires de la Société médicale des hôpitaux*, 1897, tome xiv. p. 1045.) Only one aspiration was performed in this case. No injection into pleural sac was made.

Case VII.—Béclère. Case II. (*Bulletins et mémoires de la Soc. méd. des hôpitaux de Paris*, 1895, xii. p. 42.)—Male, age not given. Extensive left-sided, intrapleural pulsation, having its maximum in left axilla. No pneumothorax, no displacement of heart. Funnel-shaped chest. Two-thirds of a liter of chocolate-colored pus withdrawn by aspiration. Great improvement thereafter. Patient living at time of report.

Case VIII., Toulmin (*University Medical Magazine*, 1894–95, vol. vii. p. 853).—Boy, aged five years. Left-sided, intrapleural, pulsating empyema. Continuance of pulsation after removal of 400 c.c. of pus by aspiration. Pneumococci in pus. Resection of portion of rib. Recovery.

Case IX.—James (*International Clinics*, 1895, 5 s., ii.). Left-sided pulsating empyema necessitatis. Large precordial pulsating tumor about four inches in diameter; its center between the third and fourth ribs. Resection of rib. Improvement. Developing signs and symptoms of phthisis pulmonalis at time of report.

Case X., Lépine (*La Province médicale*, Lyon, 1895–96, x.).—Woman, aged twenty-eight years. Pulsating serous pleurisy, pulsations being felt over false ribs on left side. Heart to right of sternum. Cessation of pulsation after aspiration.

Case XI., Roux (*La Province médicale*, Lyon, 1896, x. p. 100).—Male child, age not stated. Pneumococcus empyema, left-sided, consecutive to scarlatina. Aspiration. Reproduction of fluid, with pulsation at first intrapleural, then, with the pointing of the pus at one spot, extrapleural. Pleurotomy. Pneumothorax.

Case XII., McCosh (*Medical Record*, 1897, li. p. 156).—Male, aged thirty-seven years. Pulsating empyema necessitatis. One tumor about four inches in diameter. Marked pulsation. Portion of eighth rib resected. After operation the chest was filled with salt solution and the opening closed, whereupon the pulsation returned as vigorously as before. Great improvement after operation. Six months later the case was not progressing satisfactorily, and the patient was advised by his physician, Dr. Titus, of Hightstown, N. J., to return to the hospital in New York for further operative procedures.

Case XIII., Sallès, Case I. (*La Province médicale*, 1897, xi. p. 378.)—Male, aged twenty-seven years. Pulsating empyema of tuberculous origin. Pneumothorax. Displacement of heart. X-ray examination. Admitted to hospital February 8, 1897; died February 18, 1897, without aspiration. Autopsy.

Case XIV.—Sallès. Case II. Male, aged fifty-four years. (*Ibid.*) Pulsating empyema consecutive to traumatism. Pneumothorax. Colon bacillus in the effusion. Kicked by a horse in the left side of chest on May 5, 1896; up to that time in perfect health. Admitted to hospital June 1, 1896. Pulsation both visible and palpable over whole of left side, increasing from above downward. Heart sounds and impulse most marked at xiphoid cartilage, but extending to right of sternum. Death on June 3d without aspiration. Autopsy.

Case XV.—Dunin. The only reference to this case that I have been able to find is in Comby's monograph, in which it figures as Obs. xxviii. Comby merely states that Dr. Theodore Dunin has published in *La Gazette médicale de Varsovie* (*Gazetta Lekarska*) a case of pulsating empyema in a young person.

In the *Index-Catalogue of the Library of the Surgeon-General's Office*, second series, a case of pulsating empyema is assigned to Cavazzani (*Gazzetta degli ospedali*, 1897, xviii. p. 781). The title of the paper is "Empiema Pulsante o Peripleurite?" and Cavazzani decides the question in favor of peripleuritis. There was a tumor with expansile pulsation in the second, third, and fourth intercostal spaces close to left border of sternum. The patient had recently had an attack of pleurisy with effusion on the left side. When the tumor was present the signs of pleurisy had disappeared, and the heart was in its normal position. The patient was cured by an operation which consisted in the removal of the sternal ends of the second and third ribs and curetting the wall of the abscess. The patient was a woman, aged fifty-six years.

THE THIRD AND FINAL REPORT OF A CASE OF PRESYSTOLIC MITRAL MURMUR, COMPLICATING PREGNANCY, ETC., WITH EXHIBITION OF SPECIMEN, SHOWING TRIPLE VALVULAR LESION.

By JAMES TYSON, M.D.,
OF PHILADELPHIA.

Two previous reports have been made of this case at the meeting in May, 1899, and that in May, 1901. The patient was finally admitted to the wards of the Hospital of the University of Pennsylvania, May 13, 1902, having been working more or less at her old occupation in a shoe factory since August, 1901, about the date of her discharge from the hospital. When readmitted she was suffering from dyspnea, palpitation, precordial pain, vertigo, cyanosis, cold hands and feet, and tenderness in the epigastrium. There was moderate ascites and edema of the legs and feet. Six months previous to admission menstruation had ceased, although she was only forty years of age.

Physical examination recognized a slight prominence of the left precordial region, with the apex beat in the fifth interspace in the nipple line; also a short, feeble, presystolic thrill, and a typical presystolic mitral murmur. There was no systolic murmur audible at either the mitral or tricuspid area. It will be remembered that a systolic tricuspid murmur was conspicuous at previous admissions, but at her last admission the cardiac action was perhaps too feeble to develop these murmurs. As stated, the apex beat was in the nipple line in the fifth interspace, and the cardiac border, as determined by percussion, pointed to moderate enlargement. The liver was enlarged and tender, especially in the epigastric region.

The urine presented the usual characters of the urine of mitral disease; it was concentrated, with a specific gravity of 1029, and

deposited copiously pink urates. There was a small albuminuria and a few hyaline and pale granular casts. After this admission she did not rally as after previous admissions. There were obstinate nausea and vomiting; she gradually declined, and died on May 25th, twelve days after admission.

Two days before death there probably occurred cerebral embolism, as evidenced by numbness in the *right* arm, followed by a convulsion. The head and eyes were drawn to the left, and the left arm was in a spastic condition. Within half an hour the convulsion ceased and the muscles relaxed, though she still complained of numbness. She soon went to sleep, and next day was more comfortable, but died the following day. On the 23d she developed also signs of pleuropulmonary disease, more particularly on the right side, which the autopsy showed to be due to congestion of the lung, with incipient pleurisy, while in the upper portion of the lower lobe of the right lung there was also a sharply circumscribed dark red area, which pointed to infarction.

The autopsy was made by Dr. Hendrickson, one of Prof. Flexner's assistants, and I have the pleasure of showing the heart, which exhibits a most interesting triple lesion, confirming the diagnosis in its most important particulars. The organ weighed 370 grams, and was distinctly increased in size. Over surface of right auricle were numerous small, irregularly shaped, opaque areas of thickening. On section, considerable dilatation of all the chambers was noted. The wall of the left ventricle was decreased in thickness. The aortic cusps were thickened, so that they projected into the lumen of the aorta, and doubtless caused some stenosis as well as insufficiency. The mitral flaps were glued together and thickened, so that a buttonhole of about 1.5 cm. in length was found. The chordæ tendinæ were markedly thickened. Evident stenosis and insufficiency existed. The pulmonary leaflets were normal. The tricuspid flaps were firmly adherent one to the other and markedly thickened, producing stenosis and insufficiency.

Tricuspid stenosis, it is well known, is a rare lesion. It is commonly associated with mitral stenosis, having been found thus associated by Herrick in 138, or 90 per cent., of 154 cases collected by him. In twelve cases only did the tricuspid stenosis occur alone. I learn, too, from Cabot's *Physical Diagnosis*, that out of 87 cases

collected from the postmortem records of Guy's Hospital, 85, or 97 per cent., were associated with still more extensive mitral stenosis. My experience also accords with others, in that I failed to recognize the tricuspid stenosis before death, because of the near identity in time, quality, and position of this murmur with that of mitral stenosis. The autopsy record also points to a moderate grade of aortic stenosis, also an acknowledged complication of tricuspid stenosis. It is not, of course, impossible that the tricuspid stenosis was congenital.

Subjoined is a full report of the autopsy:

Mrs. McC., aged thirty-seven years, white; nativity, Pennsylvania. Attending physician, Dr. Tyson. Admitted May 13, 1902; died May 25, 1902, at 2.45 P.M. Autopsy May 26, 1902, at 10 A.M.

Clinical Diagnosis. Double mitral disease; chronic interstitial nephritis. Dr. Lummis, Resident Physician.

Pathologic Diagnosis. Chronic mitral, aortic, and tricuspid endocarditis, with stenosis and insufficiency of mitral and tricuspid; aortic, chiefly insufficiency, but doubtless also some stenosis; general chronic passive congestion; hypostatic pneumonia, with fibrinous pleuritis; healing infarct of lung; cardiac cirrhosis of liver; early chronic diffuse nephritis. Dr. Hendrickson, Pathologist.

Detailed Description of the Organs. Menstruating uterus; general anasarca.

External Appearance. Body that of a well-developed and fairly well nourished female; marked edema of upper and lower extremities; moderate abdominal distention; considerable cyanosis of face; moderate jaundice.

Abdominal cavity contains 300 c.c. of straw-colored fluid. Intestine reveals marked congestion of bloodvessels.

Pleural Cavities. Left contains a few firm adhesions posteriorly; no fluid. Right contains numerous adhesions, but lying between these is discovered fully 500 c.c. of straw-colored fluid, which is slightly turbid.

Pericardial cavity contains a slight excess of straw-colored fluid.

Heart. Weight, 370 grams, distinctly increased in size. Over surface of right auricle are numerous small, irregularly shaped, opaque areas of thickening. On section, considerable dilatation of all the chambers. Wall of left ventricle decreased in thickness. Aortic cusps thickened so that they project into the lumen of the aorta, and doubtless caused some stenosis as well as insufficiency. Mitral flaps glued together and thickened, so that a buttonhole of about 1.5 cm. in length is found. Chordæ tendinæ markedly thickened. Evident stenosis and insufficiency existed. Pulmonary leaflets normal. Tricuspid flaps firmly adherent one to the other, and markedly thickened with stenosis and insufficiency.

Lungs. Left lung: Posteriorly a few firm tags. Surface congested, and over lower lobe a deposit of finely granular fibrin. On section, consistency

is markedly increased throughout upper lobe and upper portion of lower lobe. Lack of crepitation everywhere, and little fluid exudes on pressure. Lower portion of lower lobe not so intensely congested, and consistence, although increased, is not so marked as that above. Right lung: Surface congested. Slight deposit of fibrin over lower portion of lower lobe. At extreme posterior and upper portion of lower lobe is discovered a dark red area 3 cm. in diameter, with sharply outlined and somewhat elevated borders. About this there is slight congestion. On section the area is found to be the base of a cone-shaped mass of increased consistence, dark red in color and limited by an opaque, yellowish, firm zone from the adjacent area of marked congestion. Throughout the lung marked congestion and increase of consistence exists, and in places early hypostatic pneumonia doubtless exists. Bronchial lymph nodes pigmented, but otherwise negative.

Spleen. Weight, 190 grams; of normal size; of stony consistence, and on section dark red in color. No increase of trabeculæ.

Gastrointestinal Tract. Marked congestion everywhere.

Pancreas. Marked congestion.

Liver. Weight, 1125 grams; decrease in size. Surface smooth, but coarsely lobulated by lines of slight depression. On section, typical nutmeg surface is revealed. Borders of lobules of a distinct yellow tint. Increased consistency.

Adrenals. Negative.

Kidneys. Weight, 290 grams; somewhat decreased in size. Capsule strips with some difficulty. Surface markings obscured. Cortex slightly decreased in thickness, and consistency slightly increased. Moderate congestion.

Bladder. Slight congestion of vessels in mucosa.

Uterus. Marked congestion of endometrium, with some increase of mucus.

Aorta. Negative.

INTUSSUSCEPTION.

With Report of a Case of Recovery after the Extrusion of Eleven Inches of Intestine.

By NORMAN BRIDGE, M.D.,
OF LOS ANGELES, CAL.

Mrs. M. L. F., a brunette, aged thirty-four years, was delivered of twins December 16, 1900. She had previously borne normally three children, all single births, and been fairly healthy most of her life. She had in 1899 for several months some hemorrhoidal trouble, for which an operation was made in September of that year, with the result of a complete cure. She also, most of her life, had a tendency to diarrhea. Slight indiscretions in diet would produce it. She had more or less diarrhea during her last pregnancy; most, perhaps, during the last few weeks of it. She was the last three months of her pregnancy extremely anasarcous. She had albuminuria, but whether casts or not is not known. During this time she was unusually dark in complexion. The confinement was without special incident and no puerperal complications followed it. But the bowels did not move after the confinement up to the time of the seizure to be described, although enemas and cathartics had been resorted to for this purpose.

On December 21st, five days after the confinement, she walked several yards to a water-closet, and was then or soon after seized with severe pain in the abdomen, soon after which a very severe spell of vomiting came on. She vomited occasionally for three days and was unable to procure a movement of the bowels. She probably vomited stercoral matter, although the history on this point is not very clear. Pain, which she declared was continuous, persisted for three days and nights, and she became extremely tympanitic and had some fever. This combination of symptoms continued for a number of days, and she was unable to take food and lost flesh rapidly. She had every few minutes for the three days of pain most violent peristaltic contractions and borborygmi.

On December 24th, after a large enema of warm water, she commenced to pass thin stools, which were, for four or five days, dark colored, almost inky, and very watery. These were the first evacuations after the confinement. She ceased thereupon to vomit, except occasionally, which she continued to

do for a week or ten days more. The meteorism gradually disappeared after the bowels began to move.

She gradually grew better, although steadily losing in weight. Her bowels moved from three to six times a day, the passages being liquid, and soon becoming grayish in color. She was up and about a little nearly every day after January 1, 1901, vomited occasionally, had great pain in the bowels, with evident severe muscular efforts on the part of the intestine, as shown by borborygmi and vermicular movements felt and observed through the abdominal wall. She did not experience a sense of relief in the abdomen by the frequent movement of the bowels, but had, after each one, a feeling as of the presence of fecal matter in the intestines seeking evacuation. The sensation was far above the rectum, and there was no tenesmus.

For four or five days prior to my first visit to her (on January 8th) she had passed frequently small shreds of what appeared to the nurse and to herself to be some form of membrane. These had not been preserved.

On January 8th she was found much emaciated, very sallow, with a slightly subnormal temperature and pulse of 96. Her lochial discharge had nearly ceased, was free from odor, and she had no uterine symptoms. There was no tenderness over the abdomen, which was flat; vermicular movements of the intestines were plainly to be seen; no tumor could be made out, but the region of the cecum was slightly tumefied and soft, and gurgled loudly on the slightest touch. An anemic bruit was heard over the heart. The deep sallowness, even bronzing of her complexion, coupled with a positive browning of the nipples and areolæ (which had grown worse within a few days), gave a strong suggestion of suprarenal degeneration. The urine was free from albumin and sugar. She had frequent abdominal pain attending the borborygmi.

She was given $\frac{1}{8}$ gr. doses of codein to quiet pain and $\frac{1}{30}$ gr. strychnin every four hours. She was promptly relieved of pain, but the diarrhea continued. At 5 o'clock P.M. of January 12th she voided from the bowels a piece of the ileum measuring 11 inches in length. I saw her the next afternoon and found no marked change in symptoms, except that the sense of incomplete evacuation after a movement of the bowels was gone completely. The peristaltic movements of the intestines were even greater than before, and a slight sense of tumor could be felt over the region of the cecum. At the next visit this had disappeared, and it did not return. No vomiting occurred afterward; the diarrhea continued for some weeks, although the gray color of the passages gradually changed to yellow; the evident difficulty of evacuating the small intestine through some narrowed opening or space grew less, and the patient developed before long a voracious appetite, and took large quantities of eggnog and soup, and after a few days began taking solid food without discomfort. There was no rise of temperature at any time.

I have seen the patient from time to time since. She gradually lost her bronzed appearance and has gained in weight until she has reached or

Piece of intestine, eleven inches long, passed by the patient. A probe is shown inserted into the lumen of the gut. Some denudation of peritoneum is shown in the left extremity, and on the right some of the wall of the intestine is gone.

exceeded the weight of the time prior to her last pregnancy (113 pounds). The difficulty in evacuating the ileum into the colon has grown less, but has not wholly disappeared; occasionally she has accumulations of gas and borborygmi in the cecal region for a few days, but no serious annoyance has resulted from this cause for many months. She still has most of the time a looseness of the bowels, with transverse colon pain just before a movement, exactly as she had before the last pregnancy.

There can be little doubt, I think, that the lesion here consisted in the invagination of a portion of the ileum through the ileocecal valve into the colon and the ulceration and liberation of the involved portion, after adhesions had been formed that were capable of preventing leakage into the peritoneal cavity.

In cases of this kind it is probably inevitable that the lumen of the ileocecal valve should be narrowed by the retained fold of small intestine, and that there should be more or less difficulty in forcing the fecal matter through. This latter function is facilitated by the generally fluid contents of the small intestine. Contraction of the cicatricial tissue after the ulceration might be expected to come on and reduce still further the opening between the ileum and cecum, but that event seems not to have happened in this case. Moreover, it is possible that the invagination was above the ileocecal valve, this organ not having been involved at all. In that case it would be natural to suppose a contraction of the tube at the point of adhesion.

The accompanying cut is from a photograph of the spread-out portion of extruded intestine. The loss of tissue at one end of it, and of the tubular character of the specimen, as well as the loss of the peritoneal covering of the other end, probably account for the shreds of membrane which the patient discharged a few days before the mass came away.

This case is interesting from several points of view. It is interesting first from the mere fact of recovery having occurred spontaneously, with detachment of the invaginated gut by ulceration, and probably without a leak into the abdominal cavity capable of producing peritonitis. This train of events is the more remarkable considering the ordeal of maternity through which the patient had just passed, as well as the sickness that had preceded this event.

It is more interesting clinically in the perfect correspondence between the symptoms—and the sequence of them—and the patho-

logic events which we know must have occurred. These were: 1. The bronzing of the skin from the irritation of the abdominal nerves that occurred in connection in some way with the early diarrhea—which last may have been simply the expression of an indigestion due to some unknown disorder of the abdominal organs, and from the intussusception and the irritation resulting. 2. The sudden seizure of pain at the moment of obstruction and on the attempt of the gut to expel the mass. 3. The persistent vomiting from the effect of the obstruction. 4. The fever from the inflammation, which also led to the paresis of the intestinal walls and the resulting tympany. 5. The flattening of the abdomen as soon as the inflammation was over and the tone of the muscular fibers was restored. 6. The marked reduction in the vomiting the moment the bowels began to move. 7. The occurrence of evacuation as soon as the inflammation subsided and the invaginated gut had, from loss of blood and failure of blood supply, probably shrunken considerably. 8. The black liquid passages, due perhaps in part to the bloody serum that must have oozed from the dead gut in the shrinking. 9. The vermicular movements and the borborygmi of the intestinal efforts to force the obstruction. 10. The expulsion of shreds of membrane as they became detached by ulceration—the sense of a foreign body left in the colon after every dejection until the large mass was finally expelled. 11. The complete disappearance of this feeling the moment the mass had been extruded. 12. The gurgling about the cecal region for days after the last-named event, and the nearly complete disappearance of this symptom later. 13. And, finally, the gradual restoration to the normal health and weight, as well as the slow disappearance of the bronzing after the known sources of irritation of the abdominal nerves had gone. Truly a more ideal clinical picture could hardly be imagined.

THE USE OF THE X-RAYS IN THE TREATMENT OF DISEASES OF THE SKIN, OF NEW-GROWTHS, OF THE GLANDULAR SYSTEM, AND OF OTHER DISEASES, AND AS A MEANS OF RELIEVING PAIN.

By FRANCIS H. WILLIAMS, M.D.,
OF BOSTON.

The use of the X-rays in medical and surgical diagnosis has now been before the profession for over seven years, and their value in this direction is more or less appreciated, their aid in surgical diagnosis being more generally recognized than their assistance in medical diagnosis. The use of the X-rays as a therapeutic agent, however, has been brought to the general attention of the profession within three or four years, and their range in this field is so wide it has seemed to me that the members of this Association would be interested in a brief outline of what they have accomplished. In the third edition of my book, *The Roentgen Rays in Medicine and Surgery*, I have considered this subject at length, and have shown how the method may be carried out and the precautions which should be taken, so that here I will confine myself more especially to some of the results of their use in diseases of the skin, in those of the glandular system, as an analgesic, and in the treatment of new-growths.

Diseases of the Skin. The first disease in which their use attracted much attention was that of lupus vulgaris. Obstinate cases of long standing were found to yield to this agent, the resulting scars were more like the normal skin than those following the use of the older methods, and parts formerly inaccessible could be reached; but experience has shown that the treatment needs to be continued over a long period if the disease is extensive and deep seated.

The value of the X-rays in the treatment of eczema, the most common of all the diseases of the skin, deserves special mention. All

varieties of this disease yield, as a rule, to the X-rays, some of them readily, and all without causing the patient any inconvenience; and, so far as my experience goes, if the disease returns it is apt to appear in some part that has not been treated by the X-rays. In addition to the relief from distressing symptoms obtained from the use of this method, the patient is likewise relieved from the annoyance of frequent application of washes or ointments; further, in some parts of the body these ointments cannot be applied in a satisfactory manner, whereas to the X-rays such portions are easily accessible.

Psoriasis, though less common than eczema, has yielded even less readily to treatment by the means heretofore at our disposal, but it responds very readily to this new agent, and although the results are not in all cases permanent, recurrences yield to the rays, and I believe that with more experience recurrences will be less apt to follow than at present.

Various forms of acne are also amenable to the X-rays, and their use in this disease—which may disfigure the face, for instance, very much—can convert a repulsive complexion into one of more than average comeliness.

My experience in treating herpes zoster by means of the X-rays has been limited to two cases; the immediate relief from the burning sensation and pain that followed their application deserves to be noted.

The X-rays are likewise useful for treating sycosis, sycosis non parasitica, favus, lupus erythematosus, nevus flammeus, etc.; but the time at my disposal is too limited to consider all the diseases of the skin in which the X-rays are of value, yet I think the instances mentioned serve to indicate that we have in them a therapeutic agent which is capable of giving relief in a larger number of these diseases than any other single remedy and to a larger number of patients when we consider the success with which it is used in eczema, for example, a disease with which so many are afflicted.

Hodgkin's Disease. Tuberculous Adenitis and Peritonitis. Tuberculosis of Lung and Bones. Now let us consider the therapeutic use of the X-rays in diseases of a different character, beginning with Hodgkin's disease, for which we have had no remedy. The X-rays offer the hope that we have in them a means of prolonging the life of the patient, and perhaps of curing some cases. In

those in which I have used the X-rays improvement in the patient's well-being and in the glands has been striking. In one case this improvement was subsequently followed by death; in another case the patient went away on a journey, and I have not since heard from him; in a third case the treatment was discontinued; the other cases are now under treatment and are all improving. Good results have also been reported by other physicians. Time will show what the final estimate of the X-rays as a remedy in this disease will be; but they certainly should be used, although cautiously, and treatment be suspended should untoward symptoms arise.

Most satisfactory results have followed the use of the X-rays in tuberculous adenitis; the so-called "scrofulous" glands, especially those in the neck, yield surprisingly well, and often quite readily, to the action of this new therapeutic agent; the same is true of tuberculous sinuses.

The treatment of tuberculosis of the lung by the X-rays is still in the experimental stage; good results have been reported as following their use by several observers, but from my own experience I am not as yet ready to offer an opinion.

Favorable results have been reported in the use of the X-rays in chronic tuberculous peritonitis.

Tuberculosis of the bone will be the least likely form to yield to the X-rays, as the calcium salts offer more obstacle to their passage than do the other constituents of the body; but in tuberculous bone the light penetrates more readily, because of its diseased condition, than through healthy bone, and this fact is an advantage in carrying out such treatment.

Diseases of the Eye. In treating diseases of the eye the X-rays have been used directly upon the cornea and also upon the conjunctiva. Some forms of severe conjunctivitis of long standing and difficult to heal by ordinary methods of treatment have been reported as having yielded to the X-rays.

X-rays as an Analgesic and Tonic. The X-rays have been found to relieve pain accompanying so many different diseases that it seems to me they are entitled to be classed among the group of analgesics, and I would again direct the attention of physiologists and pharmacologists to the study of this wonderful action of the X-rays upon the sensory nerves. We find, for example, that hepatic colic

and certain forms of neuralgia and of pain accompanying cancer are relieved by the X-rays; and that painful affections, for example, one involving the ends of the fingers, making them so sensitive that the patient could not put on gloves or use the hands with any comfort, are likewise relieved. In this case the cause of the trouble was unknown.

In the use of the X-rays I have noticed that patients not infrequently reported to me an improvement in their general well-being aside from the relief obtained from the betterment of the disease from which they were suffering. These reports have come to me independently from so many different patients that I think it cannot be an effect of the imagination, but that the X-rays have an action which may be the result of stimulation of the circulation, or, perhaps, some action on the nervous system which might be classed under the group which we designate as tonics. It is possible that this action might be helpful in some forms of cardiac disease. I have had good results following their use in nervous disease.

The X-rays are also useful in treating chronic ulcers; the action here appears to be that of a stimulant.

New-growths. The use of the X-rays in the treatment of new-growths is of special importance. A table of 150 of my patients treated by this method is given in the appendix of the third edition of my book, to which allusion has been already made. In these cases the use of the X-rays was instituted prior to 1903, and the earliest of them have been well for more than three years. My experience teaches me that in the smaller forms of new-growths and in recurrences after operation—for example, after the removal of breasts—the X-rays may be of great service. Much depends upon the size, character, and site of the growth, and whether or not the glands are involved; in the latter case the X-rays seem, as a rule, to be of less avail. Some of the smaller new-growths heal after eight or ten exposures (I have known them to disappear after two exposures), but, as a rule, the number is greater; twenty, perhaps, are needed, and in some cases a far larger number. In the latter cases great patience is necessary in order to obtain all the help that the X-rays, if their treatment is persisted in, are able to give; further, the expense is great in cases that require a large number of exposures extending over some months, and, therefore, the method in such instances is only within the reach of

the wealthy or the very poor. For the present, at least, people of moderate means would not be able to afford the use of the X-rays, outside a hospital, if their cases demanded prolonged treatment. In some instances, of course, the treatment is not so expensive as an operation; in others no more so. It is not difficult for a practitioner who has had experience to discriminate between those cases which will yield readily and those that require prolonged treatment.

Figs. 1 to 6 illustrate the beneficent effects of the X-rays.

It is too early to state in this class of diseases, as in the others already mentioned, how permanent these good results will be, but recurrences usually yield to further treatment by the X-rays.

One of the most instructive experiences that I have had in the study of the use of the X-rays in the treatment of new-growths has resulted from a group of cases which is illustrated by the following, in which I was able to compare the respective merits of the use of the X-rays and of operation. In this case an operation was done to remove a cancerous growth; three months later there was a recurrence, and a second operation was done; in less than three months a second recurrence took place; the X-rays were then resorted to. Fifteen months have elapsed since recovery took place following their use, and the patient is still well.

The breast cases form a special class by themselves. In those which are beyond the reach of operation, relief from pain may usually be had by the use of the X-rays, and the progress of the growth may be delayed. In other forms, where the growth has not gone so far, the X-rays, if used patiently and persistently, may accomplish surprising results; not in all cases, but certainly in a sufficient number to justify their employment where operation is declined. In cases where operation is considered, it seems to me quite possible that by using the X-rays persistently and cautiously during several months the progress of some new-growths in the breast might be checked, and it is not improbable that in certain of these cases the results obtained from the use of the X-rays would be as good as those which follow operation; that is to say, although the X-rays may not enable us to get rid wholly of the growth, they may give the patient as many years of life, or perhaps more, than would, on the average, follow the removal of the breast by operation. I am not ready to recommend the substitution of the X-rays for operation in these cases, but refer

to this course as one which further experience may establish as wise in certain instances. It would be necessary to carry out this treatment for a long period of time, and the plan would not be devoid of risks unless the practitioner was experienced and careful in the use of the X-rays.

In the treatment of new-growths too vigorous use of the X-rays must be avoided, in order not to stimulate the disease and so cause it to spread instead of to heal, or in the larger forms of new growths to avoid setting up a toxemia that may be disastrous to the patient.

It is evident that the X-rays promise to afford the best method of treatment for superficial new-growths, and that experience is needed, when the growths are large or deep-seated, to select the cases for which this treatment is most suitable, and that the greatest care must be exercised in order not only to avoid injurious results, but to obtain good ones; further, that the apparatus must be good and well under the control of the practitioner.

X-RAY INJURIES. There are certain dangers connected with the use of the X-rays. If the skin is overexposed, severe inflammation or even ulceration will follow, and these so-called "X-ray burns" are sometimes very difficult to heal. Another danger in their use that may occur in cases of new-growths, and Hodgkin's disease has been alluded to above, the treatment may be pushed too rapidly and a serious toxemia result; experience and care can obviate these risks.

A word as to the limit of action, as regards the site of the disease, of this new therapeutic agent. The parts most easily affected are, of course, those near the surface, but a powerful apparatus can accomplish results that are beyond the reach of a smaller one. One of my patients, the site of whose disease is the interior of the chest, lost steadily in strength, color, and weight when treated with an apparatus of ordinary power, but improved after one or two exposures when treated by means of a powerful one.

There are, then, two points to be kept constantly in mind when pursuing the study and use of the X-rays for the treatment of deeper seated portions of the body: First, the treatment must be carried on cautiously, and in many cases persistently, for a considerable period, and results looked for in some cases only after a long interval; in some cases the treatment should be interrupted from time to time and the desired results watched for during these pauses, for the good

FIG. 1.*

Case 148. G. P., aged fifty-one years. Microscopic and clinical diagnosis, rodent ulcer of nose. Duration eight years. Before treatment by the X-rays.

FIG. 2.

Case 148. G. P. After twenty-two exposures. Healing complete three days later.

* The illustrations in this article are taken from the Third Edition of "The Roentgen Rays in Medicine and Surgery," by the kind permission of the Macmillan Company.

FIG. 3.

Case 59. Mrs. S. Clinical diagnosis, epithelioma of cheek. Photograph taken after two exposures of ten minutes each to the X-rays.

FIG. 4.

Case 59. Mrs. S. After treatment by the X-rays.

Fig. 5. Case 78. A. D., aged twelve years. Microscopic diagnosis, lymphosarcoma after first operation, and round-cell sarcoma after second operation. Duration, seven years. Beforetreatment by the X-rays.

Fig. 6. Case 78. A. D., aged twelve years. After treatment by the X-rays. Still undertreatment.

effects of the treatment may be, in some instances, first observed a considerable length of time after the exposures have ceased for the time being; for instance, none may be apparent after a series of exposures given three times a week for a period of six months and then become evident some weeks after the discontinuance of the treatment. Second, the patient should in all ways be under careful observation, not only as regards the action of the X-rays on the skin, but also as regards symptoms that are the outcome of chemical changes and indicate toxemia, for example, and also by means of the methods used to ascertain what chemical changes, if any, have taken place in the urine or the blood. In a word, careful methods should be used in carrying out and controlling the amount of the treatment, and they should be employed by practitioners who have had the best training.

The action of these rays can hardly be accounted for on the ground that they kill micro-organisms; neither is it likely that all the diseases relieved by the X-rays are due to the latter; moreover, so far as experiments thus far have gone, the X-rays are not a good germicide. It seems more probable that these rays bring about some chemical changes which assist nature to cause healing and interfere with the development of some micro-organisms.

One chemical action of the X-rays is shown by the effect they produce on a photographic plate. I have observed also another effect, which undoubtedly, I think, is the result of chemical change. In my tubeholder I have used plates of glass 1 to $1\frac{1}{2}$ centimeters thick, to cover the openings in its sides, and I have noticed that where the X-rays passed through the glass the surface became of a brownish color, but where they were prevented from reaching the glass, because of the coats of white lead with which the inside of the tubeholder was painted, no change took place in the color of the glass. The discoloration of these thick plates of glass was limited at first to parts near the surface, but after longer exposure to the X-rays it extended through the entire thickness of the glass, as could easily be seen by holding the plates up to the light and looking through them edgewise. Similar changes are seen in the glass of which the vacuum tubes are made, the glass in some instances becoming of a purple color on the side through which the X-rays have passed. It is noteworthy that the color varies with the composition of the glass.

It is evident that we have in these rays a means of bringing about chemical reactions, and I believe that their therapeutic uses depend upon this property, and that by it they assist nature.

One of the most remarkable properties of the X-rays is their power to pass through healthy tissues without injury to them and bring about healing in the unsound tissues beyond them. This fact indicates the vista of possibilities that is open to the X-rays as a healing agent. We have in them a form of radiation which, within certain limits of exposure, is selective and assists the chemical processes of nature to overcome pathologic processes. It is not surprising, therefore, that the list of diseases that can be helped by the X-rays is a long and constantly growing one.

The X-rays have opened to us new methods in diagnosis, and a method for the treatment of disease more comprehensive than any other remedy we have hitherto possessed. They may also eventually prove to be a key which will assist us in studying some of the problems in the chemistry of physiologic and pathologic processes.

ARTIFICIAL IMMUNITY IN EXPERIMENTAL TUBERCULOSIS.

By E. L. TRUDEAU, M.D.,
OF SARANAC LAKE, N. Y.

Immunity against most bacterial diseases may, for convenience of study, be divided into natural, acquired, and artificial immunity. The great majority of mankind has in a varying degree a natural immunity against tuberculosis, for if it were not for this natural immunity the human race would probably long ago have become nearly extinct. In many individuals, however, this immunity is only relative, and is maintained only so long as the general health is kept at a high standard or the exposure to infection not too intense or too prolonged. An unfavorable environment, the occurrence of some other infectious disease, overwork, dissipation, or, in fact, anything that tends to depreciate the nutrition of the body, is apt to render the individual hitherto immune susceptible to the tubercle bacillus; so that it may be said that in tuberculosis, perhaps more than in any other infectious disease, environment is a prominent factor in maintaining the individual's natural immunity.

Acquired immunity against many bacterial diseases is the result of a previous attack which has been recovered from; but it must be borne in mind that this acquired immunity, like natural immunity, may vary greatly in degree and duration. At times it may be absolute and persist through a lifetime, as is the case, with rare exceptions, in variola, parotitis, yellow fever; or it may be less constant, as in measles, scarlet fever, and typhoid fever; or so slight as to afford the individual no very appreciable protection, or only to protect for a short time following recovery, as in pneumonia, erysipelas, and influenza.

In seeking to demonstrate artificial immunity we must, therefore, bear in mind that the resistance to infection, which we term immunity, may exist and yet vary greatly in degree and duration.

There is little in the clinical history of tuberculosis which shows that acquired immunity occurs in this disease, for relapse is the rule, and one attack does not seem to afford any protection for a subsequent and often fatal one. For this reason the production of artificial immunity against tuberculosis in man or animals has been always looked upon as a result never likely to be achieved. A careful clinical study of many cases of tuberculosis, however, seems to indicate at least an attempt on the part of nature at the production of acquired immunity in this disease.

We must remember that in pulmonary tuberculosis the clinical picture is obscured by the occurrence of secondary infection, which in most cases defeats the possibility of recovery, and therefore the production of any degree of acquired immunity. Even where secondary infection has taken place, however, we often note the acuteness of the process to subside without any special treatment or change of surroundings, and the disease to become arrested for a longer or shorter time and even cured, in spite of the fact that the extensive lesions already existing and the prolonged cachexia would tend to its more rapid progress to a fatal issue were not some immunizing influence at work. In acute miliary tuberculosis in man and animals the bacilli are often exceedingly difficult to demonstrate after death, and their disappearance, Koch points out, may be due to an acquired immunity, which, however, comes too late. On the other hand, autopsies show ample evidence that pure tuberculosis heals and remains healed, though the individual must many times be exposed to reinfection from outward sources. If it be accepted that 60 per cent. of all cadavers present on autopsies healed lesions, the small proportion of these which have either relapsed or become reinfected would hint at the production of a relative degree of acquired immunity. We must discriminate, however, between arrested latent tuberculosis and healed tuberculosis.

Although tuberculosis is very evidently not a self-limited disease in the same sense as the more acute bacterial infections like diphtheria, typhoid, variola, etc., we may, nevertheless, trace an attempt on the part of nature at the production of a certain degree of acquired immunity in pure tuberculosis which should encourage us in our efforts to produce artificially an increased resistance to this disease.

Artificial immunity is an attempt to imitate nature's methods of producing acquired immunity, and it is obtained by the inoculation of a modified living virus or of toxins and dead bacteria which produce the disease against which protection is sought.

Much light is being thrown on the mechanism of the various bacterial infections, and we have already learned to recognize two kinds of immunity—a toxin immunity and a bacteriolytic immunity —as the main factors in the production of any degree of acquired immunity. A true toxin immunity, as has been so brilliantly demonstrated for diphtheria and tetanus, is obtained by the injection of gradually increased doses of toxins produced by the germ on artificial media. Bacteriolytic immunity, the mechanism of which is much more complex and only now beginning to be understood, is usually induced by inoculations of attenuated but living germs, and seems to be the result of the victory of the tissues of the animal over the living germ.*

The success which was met in true toxic diseases, like diphtheria and tetanus, in bringing about protection by purely antitoxic immunity alone has tended to direct the efforts of experimenters toward the production of that type of immunization which has proved so efficient in those diseases, and the study of bacteriolytic immunity has until recently remained in the background.

Koch's tuberculin treatment represents an attempt to heal tuberculosis by the production of a toxin immunity. We know, however, that injections of the toxins of the tubercle bacilli in gradually increased doses, while it produces in the animal experimented upon a certain degree of acquired resistance to doses which if given at first would have been fatal, does not protect from subsequent inoculation with living tubercle bacilli, or produce in the animal's serum an antitoxin capable of neutralizing the minimum fatal dose of tuberculin, as has been successfully accomplished in the case of the diphtheria poison. The mechanism of any acquired immunity in tuberculosis must, therefore, be different, and success could only be attained by a different method of immunization.

* The hypothesis recently advanced by Dr. Welch would explain why a living germ is necessary to the production of this type of immunity. Dr. Welch suggests that the toxins necessary to bring about the immunity in some diseases are not elaborated by the germs while growing on artificial media, but only within the living body, in response to the stimulus of defensive substances secreted by the living cells, and which are inimical to the bacillus.

Antitubercular inoculation was first tried by Falk, in 1883, and all attempts in this direction have until recently resulted in an unbroken record of failures. In 1890[1] I added my name to the list of those who found it impossible to produce immunity in animals by this method. Dasenberg, in 1889,[2] Martin, Grancher, Courmont, and Dor, in 1890,[3] claimed to have produced a relative degree of immunity in rabbits by previous inoculation of tubercle bacilli attenuated by heat and antiseptics. Richer and Hericourt later claimed better results in dogs by inoculation of bird tubercle bacilli, but have not continued their experiments in this direction. Koch's tuberculin work, published in 1890–91, and his later paper on T. R. tuberculin, were practically attempts at immunization.

In 1892 I succeeded in producing in rabbits an appreciable immunity by inoculations of living avian cultures, and described my results in a paper read before the Association of American Physicians in 1893.[4] The immunity in my animals was shown by the fact that inoculation of virulent human bacilli in the anterior chamber of the eye of rabbits previously immunized by subcutaneous injections of avian tubercle bacilli aborted in most cases, while in the controls the eyes were destroyed.

In 1894 de Schweinitz[5] called attention to his success in protecting guinea-pigs against infection with human tubercle bacilli by means of living attenuated cultures of human origin, and to further success in protecting cows in 1896. De Schweinitz made use of the same culture with which I was experimenting, and which he obtained from me, and in 1897 I described,[6] in a paper presented at the annual meeting of the British Medical Association, held in Montreal, my results in immunizing guinea-pigs by previous inoculations of this attenuated culture of human origin. In 1901–1902 McFadyean[7] reported some success in immunizing cattle with living avian tubercle bacilli.

In May, 1902, Behring[8] published an exhaustive work describing his successful attempts at producing immunity in calves by previous inoculations of attenuated living cultures of human origin. This immunity seemed so strong that his animals resisted subsequent inoculations with a culture of bovine bacilli which killed the controls in less than six weeks. L. Pearson[9] and G. H. Gilli-

land, in November, 1902, reported their success in protecting cows by previous inoculations of living human sputum cultures.

In looking back over all the patient and tedious work which has been done in trying to immunize against tuberculosis we find that the attempts to protect animals by the production of a purely toxic immunity along the lines which have been so successful in diphtheria—attempts which were inaugurated by Koch in his work on tuberculin—have generally proved somewhat unsatisfactory, even where dead and pulverized bacilli are made use of, as in his T. R. tuberculin. On the other hand, success in protecting animals to a greater or less degree has pretty generally resulted when the protective inoculation has been made with living but attenuated cultures. The work already done would tend to establish the principle that in order to be successful the protective inoculation must be made with a living germ of such diminished virulence for the animal experimented upon as to produce a reaction ending in the victory of the living tissues over the bacilli and a complete aborting and healing of the process at first set up by them. This is termed by Behring isopathic immunity.

The attenuation of the cultures used for protective inoculations may be obtained in two ways : either by selecting a variety of the tubercle bacillus, whether bovine, avian, or human, naturally of little virulence for the race to which the animal to be protected belongs, or by previous inoculation with a variety naturally virulent for the kind of animal selected for protection, but attenuated by prolonged cultivation. Thus the cow can be protected against tubercle bacilli of bovine origin by previous inoculation with cultures of human origin, and the guinea-pig and rabbit to a greater or less extent against a virulent infection by tubercle bacilli of human origin by previous inoculations of attenuated cultures of human origin. The fact that one variety of tubercle bacillus can produce immunity against another is strong evidence in favor of the genetic unity of all tuberculous virus.

My own work, unfortunately, has been confined almost entirely to experiments on rabbits and guinea-pigs. These little animals, as Behring has pointed out, on account of their delicate organization, their intense susceptibility to the disease, and to extraneous influences which make variations in weight and temperature in

them misleading and unreliable, are eminently unsatisfactory for use in the study of artificial immunization to tuberculosis; and yet they can be immunized, if it be clearly understood that by this I mean that in them a greatly increased resistance to virulent inoculation fatal to controls can be successfully demonstrated.

I will describe as briefly as possible the main features relating to the best method which I have so far been able to devise to demonstrate with these small animals this artificially induced resistance. In some of my first experiments (in 1892) I used an avian culture subcutaneously to immunize rabbits; but this proved unsatisfactory, as the animals often died of the preventive inoculation and the germ was evidently too virulent. Later I used altogether a human culture which had become attenuated by prolonged cultivation.

All other methods of attenuation hitherto employed—heat, time, antiseptics, etc.—aim a blow at the viability of the germs sought to be attenuated, but do not alter their biologic characteristics. They are either killed, in which case they produce no disease, or else they survive sufficiently to grow in the body and ultimately destroy the life of the animal. Prolonged cultivation, on the other hand, gives us a culture which grows vigorously outside the body, but which has lost to a great extent its specific pathogenic powers.

The source of the cultures used in my experiments, and which I shall refer to as R. 1 cultures, is as follows: Cultivated on potato in 1891 by myself, direct from a case of miliary tuberculosis in man, passed through a rabbit, and grown now for nearly eleven years on artificial media, principally glycerin-peptone bouillon. This culture grows more rapidly than formerly, without presenting any marked change in appearance either in culture or microscopically. It produces in liquid media apparently as much and as efficient tuberculin now as it did ten years ago. After two years it began to show some diminution of virulence for guinea-pigs and rabbits, and after six years, in ordinary doses, it did not kill rabbits, and produced only very chronic lesions in guinea-pigs or did not kill them at all. Since then its virulence has still more diminished. This is the same culture used by de Schweinitz in protecting his guinea-pigs, and which I now show you.

The first evidence of protection which I was able to obtain from preventive inoculation with the germ was as follows: In thirty-six controls the average life after virulent inoculation was fifty-seven and two-tenths days, and in sixty-six vaccinated animals one hundred and fifty-four and three-tenths days, so that the vaccinated animals lived nearly three times as long as the controls. This includes, however, experiments made before the bacilli were sufficiently attenuated to prove harmless, and very much better results can be obtained by preventive inoculation with this culture at present.

Young animals, as Behring has pointed out, are most suitable for these experiments, as they bear the preventive inoculations much better than full-grown or old ones. The dose of the attenuated germ injected and the method of immunization adopted are of the utmost importance to success. If too little of the culture is given, protection does not ensue; if too much, the nutrition of the animal suffers, and it is likely to die ultimately cachectic and with chronic visceral lesions, especially in the kidneys. A first inoculation of a very small dose of bacilli, followed in two months or more by a second tenfold larger, has seemed to produce the best results. The culture should be weighed accurately after drying on blotting paper, and crushed so that it be as finely subdivided as possible, as the emulsion should contain no lumps of culture.

Contact with the blood stream seems necessary to success. Subcutaneous inoculation alone is not likely to afford much protection, although in guinea-pigs one subcutaneous inoculation, followed in two months or so by an intraperitoneal one, is quite efficient. For rabbits it is best to inject in the ear vein.

For a half-grown guinea-pig the initial dose should be one-eighth milligram to one one-quarter milligram of solid culture, suspended in one-half to one cubic centimeter of water, injected under subcutaneous tissue of the thigh. Little reaction follows, locally or constitutionally. The animal loses some weight for a few weeks, and the inguinal glands may swell somewhat and remain slightly swollen for several weeks. If tested with ten milligrams of tuberculin two or three months later the animals should show no reaction. An intraperitoneal injection of one-quarter to one milligram may then be given, and is usually well borne. Six weeks later the test

inoculation should be made. This should consist of a very small amount of virulent bacilli—enough, of course, to cause tuberculosis and death in the controls, but no more. In immunizing rabbits half-grown animals should be selected, and one-eighth to one-quarter milligram by weight of attenuated culture, finely divided and suspended in one cubic centimeter of water, is injected in the ear vein. Two or three months later the animal should not react to thirty milligrams of Koch's tuberculin, and if up to their normal weight may then be given the test inoculation of a half milligram of virulent bacilli in the ear vein. It is better, however, to give two preventive inoculations two or three months apart. The initial dose should be one-twentieth to one-fortieth milligram intravenously, and the second ten times greater.

No doubt these methods of preventive inoculation may be varied so as to make the immunity acquired more complete and lasting. I merely describe the plan I have adopted in attempts at demonstrating the relative immunity, and which has given me the best results so far in these small animals. Calves are much better for these studies, as the brilliant results obtained by Behring and others demonstrate.

Behring seems to have produced in calves an immunity which is so perfect that the tissues fail to react to the virulent inoculation by the formation of tubercle, and no trace of it is left on the lungs of his protected calves. In my experience with small animals the degree of immunity I have succeeded in obtaining does not prevent the local reaction of the tissues to the virulent inoculation. The eyes of my animals showed at first violent reaction, and the lungs of immunized rabbits three or four weeks after the virulent inoculation show lesions which appear even more pronounced than those produced in the controls. In the protected animals, however, the process, both in the eyes and lungs, gradually becomes retrogressive and heals slowly without any tendency to spread. In other words, in them there is a reaction, but one which is purely localized, while in the unprotected rabbits the disease steadily progresses and becomes generalized until it destroys the animal's life.

If it is evident, therefore, on one hand, that the immunity I have succeeded in producing in rabbits and guinea-pigs, though perfectly demonstrable, is only relative, it must be admitted, on

the other hand, that the flooding of these rabbits' lungs with a large dose of highly virulent bacilli is an unnecessarily trying test, and in no way comparable to exposure to natural sources of infection.

Dr. Baldwin has made this winter some as yet unpublished experiments, using Wilde's hemolytic method, on a set of calves he has immunized with attenuated human tubercle bacillus, with the object of studying the changes which occur in the serum as a result of the immunization. He finds definite proof of the presence of a specific immune body, or amboceptor, which appears in the serum of immunized animals and gradually again disappears. Traces of it were still demonstrable at least three months after the last protective inoculation.

I describe a typical guinea-pig experiment briefly: On June 10, 1902, the animals to be protected received in the left thigh an injection of one-quarter milligram attenuated T. B. R. 1 culture. Slight loss of weight followed, and on September 26th they failed to react to ten milligrams of tuberculin. They then received one milligram of living attenuated tubercle bacilli in the peritoneal cavity, which produced little appreciable disturbance of health. On January 7, 1903, they, together with five controls, received an injection of one-half milligram of highly virulent tubercle bacilli culture subcutaneously in the right thigh. The controls all died, with an average life of fifty-five days. The vaccinated animals survived, and now, one hundred and fifteen days after virulent inoculation, are in good condition. Some show at present no trace whatever of virulent inoculation, though some undoubtedly have chronic tuberculosis, as they have enlarged inguinal nodes. I have known such animals to live over a year.

These specimens illustrate some points in the intravenous inoculation of rabbits. The first bottle (A) contains the lungs of rabbits about eighty days after intravenous inoculation with one-half milligram attenuated R. 1 tubercle bacillus culture. As you note, the lungs show no lesions, and a pathologic report of these specimens, for which I am indebted to the courtesy of Dr. Eugene Hodenpyl, states that the appearances under the microscope are essentially those of healthy lungs.

This bottle (C) contains the lungs of some rabbits belonging to

the same lot, immunized at the same time, but killed twenty-two days after the inoculation of one and a half milligrams by weight of highly virulent moist tubercle bacilli culture.

In this jar (B) are the lungs of controls inoculated at the same time with the same amount of virulent tubercle bacilli culture and killed on the same day as the protected animals. You will notice that in the lungs, as is the case in the eye, the virulent inoculation produces in the tissues of protected animals at first even a more marked reaction than in the controls—so much so as to give the impression that the protected are more susceptible than the controls —but the immunity is shown by the fact that the lesions so rapidly produced tend in the protected animals to remain localized and retrogress and become absorbed. All the controls but one—a large Belgian hare—are dead, while all the protected animals which were not killed survived and are still living, one hundred and twenty days after the virulent inoculation. The average life for the five controls which died was twenty-nine days after the virulent inoculation.

Dr. Hodenpyl reports the difference between controls, Specimen B, and protected, Specimen C, as follows:

"B is a lung thickly studded with typical and cellular miliary tubercles containing tubercle bacilli, and doubtless having gained entrance into the lung through the veins.

"C is a lung largely solidified from the presence of very many masses of exudate of tuberculous origin, without definite arrangement with regard to veins or bronchi. This type of lesion more closely resembles that commonly seen in children and in some forms of acute phthisis.

"In neither B nor C is there any attempt at the formation of fibrous tissue about the tuberculous masses."

The bottles labelled "D" contain the lungs of three of the same lot of protected rabbits as bottle "C," but killed one hundred and ten to one hundred and fourteen days after the virulent inoculation. If you compare Specimen D with C you will see at a glance how rapidly the absorption of formidable lesions present in C must have gone on. It is hard to believe that these lungs, in two of which only a few tubercles appear, especially along the free edges of the lung, were once riddled with the same extensive lesions as

those of Specimen C. It is evident, therefore, that the violent reaction of the tissues to the virulent inoculation in protected animals tends to end in an aborting of the progressive tuberculous process, in the partial absorption of the morbid products, in destruction of the bacilli, and a more or less complete return to normal as far as this is possible. The rabbits when killed were in excellent condition, above their normal weight, while the average life of the controls, with one exception, as I told you, was only twenty-nine days. In many of them a few tuberculous masses were noted on the cortex of the kidney.

Dr. Hodenpyl's report of Specimens D 1 and D 2 is as follows:

"Rabbit's lung, D 1: Sections show moderate number, and for the most part tiny nodules composed chiefly of large polyhedral cells and occasionally with cheesy centers. Each nodule or tubercle is enveloped by a distinct and well-marked zone of small, spheroidal, mononucleated cells similar in appearance to the encapsulating connective tissue commonly seen in the more chronic types of tubercle. A moderate number of tubercle bacilli were found in many of the nodules.

"D 2: Section of the lung presents much the same appearance as in D 1, except that the tubercles were less numerous and even smaller in size. Tubercle bacilli could not be demonstrated in these tubercles."

It is reasonable to hope, now that this principle of immunization seems to have been fairly well established, a more thorough knowledge of the mechanism of this immunity and more extended studies may result in improved methods of protection which will reduce to a minimum the dangers of the protective treatment and produce, it may be, a more durable immunization. Behring in his last work demonstrated the absolute protection of vaccinated calves, which all remained well when exposed for months to infected surroundings, while control animals all contracted the disease. If a safe method of immunization against tuberculosis could be applied as successfully to children as Behring has proved to be possible for calves, the greatest problem before the medical profession to-day would have been solved.

What the dangers of the immunizing process are; what is the duration of the immunity produced; whether or not a living but

attenuated germ is an essential to the protective process; whether the immunity it produces may be strengthened or not by additional inoculations of any of the toxins of the tubercle bacillus or of the serum of already immunized animals; whether or not the young can be protected by the milk of immunized cows, as recently suggested by Behring ; whether or not the serum of protected animals can produce immunity of shorter or longer duration and influence favorably the course of the disease in tuberculous men and animals —all these are questions which have been opened by the demonstration of the possibility of producing artificial immunity in tuberculosis—questions of intense interest, which future research must answer.

My acknowledgments are due to Dr. Hugh M. Kinghorn and Dr. E. R. Baldwin for valuable assistance in carrying out these experiments, which were made possible through the generosity of Mrs. A. A. Anderson to the work of the Saranac Laboratory.

References.

1. Medical Record, November 22, 1890.
2. Bull. de l'Acad. de Méd., October 29, 1889.
3. Annales de l'Institut Pasteur, 1890.
4. New York Medical Journal, July 23, 1893.
5. Medical News, December 8, 1894, and Bull. No. 13, Bureau of Animal Industry, September 19, 1896.
6. British Medical Journal, December 20, 1897.
7. Journal of Comparative Pathology and Physiology, June, 1901 ; March, 1902.
8. Beitrage zur Experimentellen Therapie-tuberculose, Marburgh, 1902 ; Berliner klinische Wochenschrift, March 16, 1903.
9. Philadelphia Medical Journal, November 29, 1902.

STUDIES IN MAMMALIAN TUBERCLE BACILLI III.

Description of a Bovine Bacillus from the Human Body. A Culture Test for Distinguishing the Human from the Bovine Type of Bacilli.

By THEOBALD SMITH, M.D.,
GEORGE FABYAN PROFESSOR OF COMPARATIVE PATHOLOGY IN THE MEDICAL DEPARTMENT OF HARVARD UNIVERSITY.

Since the second communication of the writer on tubercle bacilli from different mammals, which appeared in 1898, and in which two distinct races of bacilli designated provisionally as the bovine and the human variety were defined, the study of this most important group of bacilli has not flagged. Vagedes' study of twenty-eight different cultures appeared at about the same time. The most exhaustive paper dealing with bovine and human bacilli is that of Ravenel, which appeared, with that of Koch, in 1901. Both confirmed the writer's position as to the distinction between human and bovine bacilli, but Koch went much further in maintaining that bovine bacilli do not pass to the human subject. His communication has brought out a host of responses, chiefly protests, few of which bring any more light. The most important will be again referred to in the discussion of special phases of the problem.

The following pages comprise the writer's studies subsequent to 1898. These were conducted in the same manner as heretofore, and for details the former paper should be consulted. The immediate occasion for publishing them was the isolation and study of tubercle bacilli from two cases of primary tuberculosis of the mesenteric glands in children. These cultures, designated Human XI. and XII., are of great interest, since culture XI. must be regarded as bovine in origin, while XII. is distinctively human. The other cultures described are simply in continuation of former work.

The investigation of tubercle bacilli should not exhaust itself, however, in searching for bovine bacilli in the human body. It has a much wider bearing. Only by a truly comparative study of tuberculosis in various species, both as regards the bacilli and the disease produced by them, will a firm foundation be gained for fertile studies in prophylaxis and therapy. When we consider how little has been accomplished in the etiologic treatment of tuberculosis and in defining the predisposing factors since the discovery of the bacillus, the study of tuberculosis in any and all of its manifestations must be welcome. A good illustration of this condition of things is the recent work of Behring, who, in using old, attenuated cultures in the immunization of cattle, has returned to the first method employed by Pasteur in the immunization of fowls against cholera.

For the moment, however, the intercommunicability of bovine and human tuberculosis has become the most conspicuous and pressing practical question. It has been provisionally answered in the following three ways:

1. The bovine tubercle bacillus does not pass to man because of specific host differences.

2. It does occasionally and accidentally pass to man and produce a more severe type of disease.

3. It frequently passes to man, but it becomes modified in the human body, either at once or after several transfers, so as to become unrecognizable as such.

These various possibilities were fully recognized in the former article of the writer, and they have been kept steadily in view since. The most reliance was placed upon that line of research which aimed at a solution of the question by an identification of the bovine bacillus in the human body. To what extent this reliance was justified will appear in the following pages.

Brief Description of Cultures from Different Species in Addition to Those Already Described.

Whatever deductions and inferences we may make from time to time must ultimately derive their authority from actually observed facts. The larger the number of cultures isolated and studied according to a uniform scheme, the more reliable our inferences and

conclusions. The following cultures isolated since 1898 are of interest for various reasons. Human XI. and XII., as already stated, were isolated from tuberculous mesenteric glands. Human IX. was investigated because the infection was supposed by the attending physician to have come from cattle. The cultures from dog and cat are of interest because these animals are close companions of man, and it is of importance to measure their relative susceptibility to human and bovine tuberculosis and determine to what extent human beings may be infected by them :

Human Tuberculosis VIII. For a detailed study of this culture, not included in the second paper, the reader is referred to the *Journal of the Boston Society of Medical Sciences*, 1898, vol. iii. pp. 33–38.

Human (Sputum) IX. Isolated June–July, 1899. The sputum was obtained in June, 1899, from a boy, aged twelve years, through the kindness of Dr. Millet, of Brockton, Mass., who believed that the disease was contracted from milk. (See also Bovine VIII. for additional facts bearing on this case.) The disease had been recognized about three months before the sputum was examined. In November, 1899, he had gained eleven pounds "in spite of the fact that the lungs show signs of the formation of a cavity." The boy died two years later, in October, 1901. An autopsy was not made.

The culture was isolated from two different guinea-pigs. The two stocks are designated respectively IX*a*. and IX*b*. The bacilli from both stocks grew very vigorously on dog serum from the start, and were transferred to glycerin agar after the fifth transfer without difficulty. The growth appeared upon the serum in the form of a smooth, glistening layer of considerable thickness, not unlike that of avian tubercle bacilli.

As regards form and size, the bacilli appeared rather short and straight in the original cultures, 1μ to 1.2μ long. In subsequent cultures the length was 1.5μ to 2μ and over. In staining, the carbol-fuchsin penetrated feebly in the cold, and the bacillar masses remained indistinctly outlined after the application of sulphuric acid unless the stain was applied hot.

Both cultures were tested on guinea-pigs and rabbits, as shown in Table I. The rabbit inoculated with IX*a*. increased in weight, and when chloroformed after three months showed in the lungs several small patches of tubercles on the extreme cephalic edge of the cephalic lobe symmetrically situated on both sides.[1] In each kidney there were some necrotic purulent radial striæ extending from the cortex into the pelvis.

The rabbit inoculated with IX*b*. at the same time succumbed in twenty-eight days. There was marked emaciation. The lungs were of a rosy color,

[1] This peculiar localization of tuberculous lesions following intravenous injection of tubercle bacilli in rabbits is not so rare, and is suggestive when compared with the seat of incipient pulmonary disease in the human subject.

edematous, but they collapsed well. They were permeated with countless minute, grayish translucent points. Similar gray points were found in the liver and a few in the cortex of the kidneys. Unfortunately a repetition of the animal test with IX*b*. was made impossible by the loss of the culture. Subsequently two rabbits were inoculated with IX*a*. recovered from a rabbit. Both were but slightly affected, and had to be chloroformed after two and three months, respectively. The effect upon rabbit No. 40 (see Table I.) is probably explainable as the result of a larger dose given by accident in this case acting upon a more susceptible animal. The effect upon guinea-pigs throughout was that of a human culture of normal virulence, and there was no reason to regard the two stocks as different, since morphologic and cultural tests agreed perfectly. The characters of this culture may be summarized as follows:

Bacilli of medium length (1μ to 2μ), which grew very vigorously from the start. Their pathogenic power is not above that common to cultures of human origin.

Human X. Isolated February 15, 1902. The following portion of the autopsy notes bearing upon the tuberculous lesions was kindly furnished by Dr. J. H. Wright, Director of the Clinico-pathologic Laboratory of the Massachusetts General Hospital:

"*Autopsy* No. 812. . . . The body of a woman, aged forty-six years, 160 cm. long, emaciated. Pleural cavities largely obliterated by connective tissue adhesions. Left lung more voluminous than the right, and generally resistant to the touch. The superior lobe firmly grown to the inferior lobe by fibrous pleural adhesions. The superior lobe, on section, presents two large cavities in the apex. A portion of the wall of one consists of little more than pleura. The larger of these cavities is, perhaps, 5 cm. in greatest diameter. The smaller is, perhaps, 3 or 4 cm. in greatest diameter. The walls of these cavities are fairly smooth, and there is adherent to them a thick, yellow, purulent material. The lung tissue bordering upon these cavities is indurated, more or less fibrous, and blackish in color. It is not certainly determined whether these cavities represent greatly dilated bronchi, or represent excavations in the lung substance. . . . The substance of the superior lobe is generally more resistant to the touch than normal, and of a dirty grayish to blackish color, and of a more or less fibrous appearance. In places yellow, opaque areas are present on the cut surface. The entire inferior lobe is more resistant to the touch than normal, and on the cut surface appears thickly sown with discrete and confluent, grayish, granular nodules, about pin-head in size, which project above the cut surface. The lung substance between these nodules is dark red, moist, and infiltrated with fluid.

"*Right Lung.* The apical portion of the lung and the neighboring portions lying immediately beneath the pleura are transformed into a blackish, more or less fibrous tissue, in which numerous yellow, opaque areas or small cavities, containing thick, yellow, purulent material are present. The largest of

these cavities is about 1 cm. in diameter and lies at the apex. This layer of lung substance so changed extends at its deepest portion from the pleura into the lung substance for a distance of, perhaps, 2 cm. The remainder of the superior lobe contains few or no lesions. In the inferior lobe of the right lung, over an area, perhaps, of 5 cm. in diameter, the lung substance on section presents the appearance of containing rather numerous discrete and confluent, pin-head-sized, yellow, opaque nodules." . . .

Three guinea-pigs were inoculated with suspensions of lung tissue from the inferior lobe of the right lung. The comparatively mild disease induced in these—for in all there was an increase in weight after the inoculation—made me anticipate a culture of a low degree of virulence, which anticipation proved true. From two of these guinea-pigs horse-serum tubes were inoculated, and in all tubes a very rich growth subsequently appeared. The test inoculations were, however, made with subcultures of but one stock.

The bacilli from both dog and horse serum were slightly curved rods from 1.5μ to 2.5μ long, the larger number about 2μ in length. In pathogenic power this culture was like most of the human cultures studied. The two rabbits which received the standard dose[1] into an ear vein were chloroformed after two months. There were no visible tubercles whatever in the lungs of one rabbit (115). In the other there were small groups of minute tubercles along the free border of the cephalic and ventral lobes. In the kidney a few foci were found. The rabbit receiving the same dose under the skin was chloroformed after two and two-thirds months. In addition to the local lesion there were a few flat, grayish infiltrations in the thin border of one cephalic lobe, and scattering nodules in the other lobes of the lungs. The effect on guinea-pigs was equally moderate, as shown in Table II.

This bacillus thus presented all the characters of the human type—about 2μ long, easily cultivated, and producing in rabbits a comparatively mild disease.

Human XI. Isolated March, 1902, through guinea-pigs from the mesenteric glands of a child. The child was admitted to the Children's Hospital, Boston, Mass., in December of 1901. I am indebted for the material to Prof. Mallory, and for the following facts taken from the clinical and autopsy records to the hospital authorities, and more particularly to Dr. Hoag, who performed the autopsy:

"A. R., male, aged three years, an only child of parents who are well. He was nursed for three months after birth, then fed on milk and water, mixed in varying quantities. He has had diarrhea and vomiting during the past month. One week ago a sudden onset of fever, vomiting, and convulsions. Has been very sick since.

"*Physical Examination.* Well developed and well nourished. Head, normal; eyes, normal; tongue, coated; throat, slightly red; neck: no glands; chest: sides move equally on palpation; râles can be felt over both front and

[1] 0.5 c.c. of a sedimented suspension about as dense as a 24-hour bouillon culture of the typhoid bacillus. This is approximately equivalent to one milligram of moist bacilli.

back; resonance good except at right back, where there is dulness; fremitus increased, both tactile and vocal; bronchial breathing; râles numerous, of coarse variety for the most part, some dry crackling; heart sounds clear, no murmurs; abdomen rigid, apparently tender, but no distinct point of tenderness made out; no dulness."

During the period elapsing between date of admission and death, which took place February 6, 1902, the temperature remained fairly high, touching 104° F. several times. The condition of the lungs remained nearly unchanged. Toward the end diarrhea set in and there was much dyspnea.

Autopsy, by Dr. Hoag, fourteen hours postmortem. . . . "Abdomen much distended, irregularly tympanitic. On palpation the lower edge of the liver is felt about 3 cm. below the costochondral border. An irregular tumor is palpable in the central part of the abdomen. A mass about the size of a small orange may be felt on deep palpation; it is irregularly round and noduled, and cannot be moved about. Apparently disconnected with this mass is a second tumor, running transversely. It is sausage-shaped and extends clear across the abdomen just above the umbilicus. It feels 3 cm. or 4 cm. wide, and is quite even throughout and also immovable.

"*Peritoneal Cavity.* On cutting through the abdominal wall the knife enters at once a boggy, friable, irregularly softened, yellow-gray tissue, which is the cross-section of the transverse tumor mass. Thus, what was supposed from palpation to be the transverse colon packed with fecal matter, is in reality an entirely abnormal product, occupying the site of the subperitoneal fatty tissue. It is inseparably connected to the peritoneum throughout the most of its course across the anterior abdominal wall, though in places it may be quite readily stripped therefrom. Numerous irregular septa of a similar composition are reflected backward between the coils of intestine. All the coils are adherent to one another, joined by a cementing substance of peculiar nature. In some places it is composed of short fibrous bands; in others it is slightly elastic, yellowish gray in color, and may be peeled off in imperfect casts of the gut. In most places the union is by a gray-yellow substance, readily peeling away and crushing easily under the fingers. A few small caseous areas are seen where the cement substance is thickest. Many yellow-gray lymph nodes of all sizes are found in the mesentery, some showing irregularly softened centers. Indeed, the central tumor mass is apparently composed of a closely-packed group of retroperitoneal glands with mesentery. and cementing exudate binding all firmly together. The tumor thus formed is 6 x 6 x 7 cm.

"The liver is attached to the lower surface of the diaphragm by strong fibrous bands, also by gray, friable, elastic exudate. The spleen is likewise bound down on all sides by fibrous adhesions. The cecum is in the right iliac fossa. Appendix not found.

"*Pleura.* Left pleural cavity normal. Right pleural cavity obliterated by general fibrous and gray, friable exudate, about one millimeter thick.

"Pericardium normal; contains about forty cubic centimeters of clear, straw-colored fluid.

"*Right Lung.* On removing the fibrous exudate many translucent, gray, elevated areas are seen throughout the pleura. They are 2 x 2 mm., hard to the touch, and evenly distributed over the surface of the lung. On section the ground color is purple-brown, dotted with scores of tubercles similar in size and general appearance to those beneath the pleura. The whole lung is non-crepitant, but floats in water. From the alveoli and bronchi much clear fluid flows. A few bronchi contain puriform material. In the right lobe anteriorly is an irregular, depressed area, semitranslucent. On section it is non-crepitant and edematous. The bronchi are here filled with gray, puriform fluid.

"*Left Lung.* Pleura normal; in other parts it is similar to the right, but a small amount of lung tissue is still air-containing. The tubercles are less numerous than in the right. Peribronchial lymph nodes normal. . . .

"*Gastrointestinal Tract.* Stomach normal; in small intestine are a few round or oval ulcers, chiefly upon the Peyer's patches, from 0.5 mm. to 8 mm. across. The excavation is 1 mm. to 2 mm. deep, with irregular floor and raised margin, with strikingly little circumferential injection; colon normal; pancreas normal; liver: weight, 620 gm.; surface, already described. On section, reddish brown, very light in tint; lobules are very indistinct; the cut surface is oily and glistening; here and there are yellow-gray points, 1 mm. across; considerable injection just beneath the capsule, appearing as many small red points and radiating lines; gall-bladder filled with brown, viscid bile. . . . .

"Organs of neck not removed; head not opened.

"*Anatomical Diagnosis.* General tuberculous peritonitis; tuberculous adenitis (mesenteric and postperitoneal lymph nodes); tuberculous ulcers of small intestine; perisplenitis; perihepatitis (fibrous and fibrinous); fibrous and fibrinous pleuritis; miliary tuberculosis of lungs; edema of lungs."

The mass of mesenteric lymph nodes was the source of the bacilli isolated. On section they were found caseous, the center quite soft and easily scraped away. The cheesy scrapings contained large numbers of tubercle bacilli, fully 2μ long, and even longer. A few stained solidly; many appeared granular, fragmented. They were frequently in groups of three or more individuals, ranged parallel to one another. The softened, cheesy masses were suspended in normal salt solution and injected into the peritoneal cavity of three guinea-pigs. Cultures on glycerin agar made at the same time were found overgrown with miscellaneous bacteria next day.

Tubercle bacilli were isolated from two of the inoculated guinea-pigs chloroformed for the purpose. These we will call respectively XI.*a* and XI.*b*. The isolation and subsequent cultivation were attended with difficulties. Horse serum failed entirely. On dog serum feeble growths were obtained after four or five weeks of incubation, and for five months thereafter the multiplication was very feeble. Efforts to obtain more than a precarious

growth on glycerin agar did not succeed until after eight or nine months. On dog serum the earliest cultures appeared as a very thin, moist, veil-like, grayish layer. It was easily removed with a platinum wire as a grayish semifluid, not viscid or cohesive mass, and readily spread on cover-glasses. In some tubes the growth appeared as an aggregation of minute colonies. The bacilli from all cultures examined were plump rods, many of them thick, centrally and tapering somewhat toward both extremities or slightly thicker at one end and tapering toward the other. They were straight or very slightly curved. Measurements from various cultures showed that they varied from 1μ to 2μ in length, the majority being about 1.5μ long.

The effect of culture XI*a*. upon rabbits and guinea-pigs fell but a trifle below that of bovine bacilli in virulence. Similar tests were made several months later with culture XI*b*. upon rabbits with the same result. (Table I.) In all rabbits receiving the standard dose into an ear vein the lungs were found permeated with minute, grayish, translucent tubercles, some with opaque necrotic center. The rabbits lived a trifle longer than those which receive the same dose of bovine bacilli. In two cases they were chloroformed because of severe dyspnea. The lungs after death collapsed somewhat more than is the case with rabbits receiving bovine bacilli. With the latter the tubercles grow so rapidly that the animal succumbs before the dyspnea is pronounced. After death the lungs remain expanded, probably owing to the presence of so many tubercles. These differences are not sufficiently marked to deserve more than passing notice.

Culture human XI. thus differs from the human type or variety in its short, straight form, in its feeble growth upon the most favorable media, and in its much higher pathogenic power toward rabbits and guinea-pigs. Its effect upon cattle and certain cultural characters will be described later on.

Human XII. Isolated April, 1902, by passage through guinea-pigs from the mesenteric glands of a child. The child (C. M.), aged two years and nine months, was admitted to the Children's Hospital January 21, 1902, from the records of which institution the following notes were kindly furnished:

The child had been sick for three months prior to her admission, during which period there was moderate painless swelling of the abdomen. During the last month the swelling had increased and pain had appeared. For one month diarrhea was present, but latterly the bowels were regular. Family history negative. The clinical diagnosis of tuberculous peritonitis having been made, an operation was performed by Dr. Burrell on January 30th. The child grew steadily worse, and died March 11th. I am indebted to Dr. Hoag for the following autopsy notes, of which those sections are omitted which do not bear directly upon the tuberculous lesions found:

". . . *Peritoneal Cavity.* The parietal peritoneum is so adherent to underlying structures as to necessitate the removal of the abdominal contents and the right lung *en masse*. This is possible by stripping the peritoneum and the pleura from the body wall. On subsequent dissection many

fibrous bands are found binding adjacent viscera together. The parietal peritoneum is evenly and profusely dotted with firm, pearly-gray bodies 1 mm. across. Many small, gray, roughened thickenings of the parietal peritoneum mark the site of short, tough, fibrous filaments, which passed to the parietal peritoneum beneath. But little parietal peritoneum remains normal. Upon the peritoneal surface of spleen, liver, and intestine are many irregular, nodular, yellow-gray, caseous lesions, from 2 mm. to 10 mm. across and 2 mm. to 3 mm. high. Large caseous masses are found, which appear to be formed by fusion of these smaller masses. Many of the natural 'cul-de-sacs' of the peritoneum are obliterated, so that movable viscera are rendered immovable. Upon the serosa of the gut are many similar caseous nodules more uniform in size. They form irregular, hemispherical, sharply differentiated, yellow-gray elevations 3 mm. to 5 mm. across. Their tops are flattened and covered with roughened peritoneum. They are firm and unevenly granular, being composed of numerous, closely aggregated, yellow-gray, spherical tubercles embedded in translucent, gray, fibrous tissue.

"The peritoneum covering liver and diaphragm is profusely dotted with translucent gray tubercles. Fewer tubercles occur upon the spleen and serosa of the gut. The mesenteric and retroperitoneal lymph nodes with the matted mesentery form a flattened, ovoid, nodulated tumor mass 10 x 8 x 4 cm. The individual lymph nodes range from the size of a bean to that of an English walnut. Some are smooth of surface, firm and yellow on section, with but few softened, yellowish areas within. Others are of irregular contour, soft and doughy, with cheesy, yellow-gray, or with creamy, puriform contents. Microscopic examination of the softened material reveals many tubercle bacilli and much poorly-staining, granular detritus. Irregular, firm, beaded cords of fibrous tissue traverse the mass in all directions. Numerous uneven, flattened, yellow-gray, caseous thickenings, somewhat separated from the general mass, occur in the mesentery. Cecum and appendix involved in the general process. Appendix hidden in a mass of adhesions.

"*Pleural Cavities.* Left normal. The right is obliterated by the profuse and general development of gray, fibrous adhesions, bearing conspicuous bright red bloodvessels to the thickened parietal pleura. The two pleural surfaces are thus loosely united by tough, injected, fibrous filaments. The parietal pleura is 2 mm. to 3 mm. thick. It is leathery and yellowish gray in color. Its external surface presents low, curved ridges opposite the costal spaces. Its inner surface is roughened and supports the organized fibrous filaments above mentioned. Section of the thickened parietal pleura shows a few small, irregular cavities 1 mm. to 3 mm. across, containing yellow, cheesy detritus. On dissection the parietal pleura and fibrous tissue may be peeled with difficulty from the visceral pleura. The visceral pleura thus laid bare is but slightly roughened and not thickened. Immediately beneath the visceral pleura of each lung are seen many pearl-gray, glistening tubercles. . . .

"*Mediastinum.* Small, irregular, flattened nodules occur in the loose areolar tissues. Thymus normal.

"*Left Lung.* The upper lobe is small, being but one-fourth the size of the lower. With the exception of the anterior margin, the upper lobe is uniformly non-crepitant and leathery. On section it is light gray, tinted with brown, marked by a few pearl-gray tubercles, rarely occurring in small clusters. On gentle pressure much gray, creamy, puriform fluid oozes out from the bronchi. The rest of the lung is light gray and crepitating, containing numerous miliary tubercles, singly and in groups. Bronchi everywhere contain mucopus, with but little injection of the mucosa.

"*Right Lung.* Right lung, with the exception of the apex, normally crepitant. Color light gray, with slight carbon tracery, forming a fine-meshed checkering. The apex is red-brown and roughened upon the surface by fine pits and furrows. The apex is non-crepitant and solid. On section the central portion of this part is uniformly solid, and mottled by closely grouped, light mahogany areas 5 mm. across, showing considerable injection. Between are ill-defined zones of lighter tint. The central consolidation yields no fluid on pressure, except from the bronchi. The peripheral zone of the apex consolidation is brown-gray. On gentle pressure considerable turbid, gray fluid oozes from the lung substance, and much creamy gray exudate flows from the bronchi. The cut surface of the rest of the lung is of normal color. Miliary tubercles, either scattered or grouped, project from the frothy lung tissue. From the smaller bronchi oozes puriform exudate. Peribronchial lymph nodes normal.

"*Gastrointestinal Tract.* Stomach slightly injected, and contains a little mucus. Large and small intestines show many ulcerations, 2 mm. to 5 mm. across, communicating with caseous nodules upon the serosa of the gut. About these ulcerations is slight injection of a slightly elevated margin; often the mucosa is irregularly puckered. The ulcer has no floor but the caseous contents of the softened tuberculous lesion of the serosa. Many small, round, caseous areas of the peritoneum have invaded the middle layer of the gut and form dome-shaped elevations beneath the mucosa. All stages of this sinus formation occur, from nodular, tuberculous thickenings of the serosa without invasion of the muscularis, to protrusion into the lumen of the gut of a caseous mass, covered by thin, transparent, glossy, mucous membrane, threatening immediate perforation. No primary tuberculous ulcers found. . . .

"Deep in the spleen are a few firm, sharply circumscribed, yellow-gray nodules 2 mm. to 4 mm. in diameter. Considerable increase in consistency.

"*Anatomic Diagnosis.* Tuberculous peritonitis; tuberculous pleuritis (right); miliary tuberculosis of the lungs; atelectasis; confluent bronchopneumonia (right apex); conglomerate tubercles of the spleen; intestinal ulcerations (secondary to caseous nodules of the peritoneum)."

In this case the autopsy notes point to a primary tuberculosis of the mesenteric lymph nodes, followed by an eruption of tubercles on the peritoneum,

the pleura, and in the lungs. The mass of fused tuberculous mesenteric lymph nodes was the source of the culture to be described. A suspension of necrotic tissue from several nodes in which the bacilli were very scarce was injected into the abdomen of two guinea-pigs. Cultures made directly from the softened centers of these glands on dog serum and glycerin agar remained sterile. Both guinea-pigs were chloroformed at the end of four and five weeks, respectively. The lesions were those of tuberculosis, but they were of only moderate severity.

Cultures were made on dog serum and horse serum from lung, spleen, omentum, and liver of both animals, and within three to four weeks a very vigorous growth was present on nearly every tube inoculated. The bacilli in the earliest cultures were rather plump, slightly curved rods, varying from 1.5μ to 2μ in length. In subsequent cultures, both on dog serum and on horse serum, they were 2μ to 2.5μ long and slightly curved. There was no difficulty in speedily obtaining rich growths on glycerin agar and on the surface of glycerin bouillon.

The pathogenic effect of this culture on rabbits was slight, as shown in the table. The rabbit (122) receiving the horse-serum culture was chloroformed after three months, during which a slight increase in weight had taken place. In the lungs a few very small, translucent tubercles were found. In the kidneys about six foci had extended from cortex into pelvis, where a little pus indicated affection of the pelvis. The iris of both eyes contained small, gray tubercles. The rabbit (132) receiving the dog-serum culture was killed at the same time. No tubercles were seen in the lungs. In liver and kidneys a few small, gray tubercles were found. In a third rabbit (135) inoculated over four months later the effect was equally slight. In both lungs only three tubercles 0.5 mm. to 1 mm. in diameter were found. In the kidneys a small number of radial necrotic striæ, with still normal pelvis. Scattering, opaque, white tubercles in walls of cecum. Eyes normal.

The parallel inoculation of guinea-pigs with the same cultures resulted in prolonged disease indicative of a rather low degree of virulence. In conclusion it may be said that this culture bore a striking resemblance to human culture X. in all details.

Bovine Culture VIII. Isolated July 17, 1899, from a tuberculous mediastinal gland of a cow. This animal belonged to the family of the boy from whose sputum the culture designated human IX. was isolated. The culture was sought as a parallel to the latter because of the suspicion entertained by the boy's physician that his disease was of bovine origin. This cow could not have been the source of the infection, for it had been received in exchange for another cow three months before, and the boy's illness dated back at least three months. Any definite information concerning the preceding cow was lacking, but the absence of tuberculosis in the immediate surroundings of the boy led to the hypothesis above quoted.

The cow furnishing the material for Culture VIII. was examined by Dr. A. W. May, who reported extensive disease of the lungs, pleura, and thoracic

lymph nodes. The mesenteric nodes were also affected. The udder and associated lymph nodes were not visibly diseased. The bacillus was isolated through guinea-pigs. Cultures from two of them grew feebly and slowly through a number of transfers. The bacilli were short, straight rods 1μ to 1.5μ long. The pathogenic power of this culture upon rabbits and guinea-pigs was equal to that of the bovine cultures heretofore studied, as shown in the tables.

Cat Culture II. Isolated April, 1900. Several guinea-pigs were received from Dr. Langdon Frothingham, who had inoculated them from a tuberculous mediastinal lymph node. He found numerous isolated tuberculous foci in the lungs of the cat, but no abdominal disease. No information as to the probable source of the infection was obtainable. In cultures the bacilli were not identical either with the bovine or the human type. They were a trifle longer than bovine bacilli (2μ). The virulence as manifested on rabbits approximated that of the bovine type, but did not quite attain it. Unfortunately, the culture was lost after the early tests, and hence these could not be repeated. Both rabbits inoculated with the standard dose into an ear vein died early, but in one there was a peculiar necrosis of the appendix. It was greatly thickened and had a homogeneous, yellowish appearance. I assume that this was not due to the injection. In both rabbits the lungs were permeated with very minute, grayish, and opaque, whitish tubercles, but both collapsed nearly to normal, differing in this respect from the lungs of rabbits inoculated with bovine bacilli, which collapse only slightly or scarcely at all when the thorax is opened.

In endeavoring to place this bacillus, we have two alternatives to choose from: Either the bacillus is bovine in origin and modified in virulence by passage through the cat, or else it is a variety adapted and belonging to the cat as a species.

Cat Culture III. Isolated April, 1901, from lungs sent to me by Dr. J. F. Winchester, of Lawrence, Mass. According to Dr. Winchester, this cat was much in the company of a tuberculous patient who died in December, 1900. Another cat, a male, from the same family, chloroformed and examined because suspected of being tuberculous, was found free from disease. The tuberculous cat showed marked symptoms of disease before she was killed. She was emaciated and failed to eat her food. Her respirations were short and varied in frequency. Dr. Winchester did not report any disease of the abdominal organs.

The lungs had a very peculiar appearance. The entire surface of the various lobes showed a meshwork of broad bands, grayish in color, with a faint yellowish tint here and there. They did not project appreciably above the surface. The little surface left in the spaces of this meshwork was dark red. The appearance suggested an infiltration of the subpleural lymphatics. On section, however, these bands were seen to be the surface of large, coalescing, tuberculous foci of a grayish to yellowish color, which involved the greater part of the lung tissue. An examination of fixed and hardened tissue

showed a dense filling up of the alveoli, with rather large cells, which resembled desquamated alveolar cells, but which were evidently true epithelioid cells. Giant cells were absent. The dense masses of epithelioid cells were invaded by polymorphonuclear leukocytes, which in some places formed abscess-like foci. The usual necrosis of the epithelioid cells associated with tuberculosis was seen only in traces here and there. There was also some slight infiltration of lymphoid cells among the epithelial cell masses. Along the large bloodvessels they formed a sheath, but the air tubes and peribronchial tissue were not affected. In the focal areas the alveolar walls were barely recognizable, having been probably destroyed by the intra-alveolar pressure exerted by the new growth of cells. The bacilli, as seen in smears from the lung tissue, were few in number. They appeared in groups of very slender rods, staining very feebly and recognized with difficulty.

From a suspension of the scraped and teased tissue three guinea-pigs were inoculated, from one of which the culture was obtained. The bacilli after the first transfer assumed the bovine form; that is, they were quite short and thick, and the majority about 1μ long. The cultures developed slowly and grew feebly for a number of transfers. In tubes of dog serum the growth had for a time a smooth, translucent appearance, somewhat like that of the avian race.

The virulence tests upon guinea-pigs showed from the start a degree of pathogenic power much lower than that of the bovine race. Those upon rabbits yielded no uniform results. The two first were, contrary to custom, put under chloroform before the injection was made into an ear vein, and I attribute the rapid death to a different distribution of the bacilli than would have obtained without the anesthetic. Before death there was evidence of marked toxemia only rarely seen. The eruptions in the lungs were moderate, and did not approach those of the bovine race. The liver, on the other hand, was invaded to a greater extent than is usual. The third rabbit died within seventeen days, but there were no visible lung tubercles whatever, and in the fourth the inoculation disease was complicated with septicemia or "snuffles." The fifth rabbit gained considerably in weight during the two months following the inoculation. When chloroformed a moderate eruption of tubercles was found in the lungs. This culture may be characterized as identical with the bovine race in morphology. In pathogenic power upon guinea-pigs it was not appreciably above that of the average human race. As to rabbits the results are somewhat contradictory, but they indicate a slightly increased activity as compared with human cultures.

Dog Culture I. Isolated May 1, 1899. *History:* Portions of the viscera of a dog were received from Drs. Peters and Parker, of the Massachusetts Board of Cattle Commissioners, in April, 1899. The history of infection could not be clearly made out. The dog had had the opportunity of eating offal from a slaughter-house conducted by his owner, and he had also been exposed to a supposedly phthisical man, his keeper.

From the organs sent the following notes were made: Liver (small piece) contains nodules up to 2 mm. diameter, and a focus 1 cm. to 2 cm. in diameter,

with caseous center. (The entire liver was reported involved). Omentum densely sown with tubercles, from mere specks to several millimeters in diameter. One aggregation of tubercles is several centimeters in diameter. A similar mass on the diaphragm. In two lobes of the lung sent, a large number of translucent miliary tubercles; the pericardium thickened, opaque; the adherent mediastinal membranes studded with many tubercles 1 mm. to 2 mm. diameter. The ventricular wall of the left side of heart contains large, well-demarcated, whitish foci, having a medullary appearance and without the macroscopic signs of necrosis. The left auricle completely involved in a similar lesion, so that normal wall was no longer recognized. Both auricle and ventricle of right side contain similar foci. Judging from the distribution and age of the lesions, and in default of more accurate information, we may regard this case as due to food infection. The bacilli probably were disseminated over the peritoneum from a cheesy mesenteric gland, and absorbed into pleural cavity through the lymphatics of diaphragm. The heart and lungs were probably infected from the hepatic circulation.

The lesions of the mediastinal membrane, the lungs, liver, and heart, were subjected to microscopic examination in paraffin sections. The larger tubercles in all these tissues presented certain peculiar characters to which I wish to very briefly call attention. Perhaps the chief feature was the uniformly necrotic, homogeneous, central mass, staining with eosin and other acid dyes, which was almost completely devoid of chromatin particles indicative of nuclei destruction. It had an indistinctly fibrillated appearance, the fibrillæ being most distinct in the periphery and arranged more or less circularly. Outside of this necrotic, circular, or elongated center was a zone of more or less distinctly spindle-shaped cells, irregularly arranged into a network. The zone bounding this consisted of circularly disposed bundles of connective tissue fibers. The necrotic center in some situations sent spurs into the outer living zones. The larger tubercles in all the situations examined presented these same features. Giant cells so characteristic of spontaneous bovine and human tuberculosis were wholly absent. In the lungs the submiliary tubercles present the usual central mass of epithelioid cells in which rarefaction is already begun. A small number of lymphoid nuclei are among them. Only a few tubercle bacilli were found in these lesions after prolonged search. They were slender, slightly curved rods, measuring up to 6μ in length. The longest may have been pairs.

Three guinea-pigs inoculated with tubercles from lungs and omentum all developed tuberculosis, but the resulting disease indicated but few living bacilli in the material inoculated. Cultures were isolated from two of these, which were in all respects identical, both as to morphologic and cultural characters, so far as examined. The cultures from the spleen and omentum of the guinea-pigs on dog serum became very rich within two weeks. In fact, the rapidity of multiplication was perhaps even greater than with the average human culture. In form they were straight rods 1.2μ to 2μ long—*i. e.*, not quite so short as the bovine type.

The two stocks were inoculated into guinea-pigs and rabbits under almost

identical conditions. The guinea-pig of one stock died in twelve days; the two from the other died on the same day (twenty-five days). As regards the rabbits, the result from the two stocks was practically identical. Both had gained slightly in weight when chloroformed. In the first there was only a small number of tubercles in the free lateral margins of the lungs, and some radial foci in the kidneys. In the second the tubercles were scattered more uniformly over the lungs, but even at this date (two months and five days after inoculation) they were merely point-like in size and translucent, glassy. Only a few with an opaque center. The kidneys were the same as in the first rabbit.

This culture may be characterized as follows: Bacilli grow richly on dog's serum from the start. Rather short, straight, 1μ to 2μ long. The virulence toward guinea-pigs does not approach the bovine type. Rabbits are but slightly affected. In this respect the virulence is equal to, or even below, that of the human type.

A few points concerning the cultures thus briefly described may be here brought together in the interest of the reader.

The two human cultures, one (IX.) from sputum, the other (X.) directly from lung tissue, agree closely with one another and with the human type as most frequently encountered.

The two cultures (XI. and XII.) isolated from the mesenteric lymph nodes differ markedly from one another. XI. approaches, but does not quite attain, the virulence of fresh bovine cultures. Its morphology is that of the bovine race. XII. is essentially of the human type and agreeing with X. in all respects. It is significant that these two quite divergent races of tubercle bacilli were associated with diseases very much alike in the human subject.

The results of the study of human IX. and bovine VIII., the former from the sputum of a boy, the latter from a cow owned by the family of the boy, indicate no relationship between these cultures. Bovine VIII. was a typical bovine bacillus and human IX. with the usual characters of human bacilli.

The two cultures from cats show some differences. The bacilli from cat II. were much more virulent than those from cat III. Both approximated the bovine bacillus in morphology. The environment of cat III. suggests infection from man, but certain tests to be described later do not warrant this classification, but intimate a closer relation to the bovine bacillus.

The culture from the dog resembles in most respects the human type, but unfortunately the early loss of the culture prevented the use of other tests required to place this bacillus more definitely.

TABLE I.—Showing the result of the inoculation of rabbits with the various tubercle bacilli in pure cultures.

Designation of culture.	Total age of culture.	Number of transfer.	Age of culture used in days.	Dose in c.c.	Number of rabbit.	Date and mode of inoculation.	Initial weight, grams.	Final weight, grams.	Result.	Remarks. (For brief description of lesions, see notes under each culture, pp. 111–123.)
Human IX.*a* (sputum)	1 mo. 18 days	3d	9	0.5	41	Aug. 9, 1899 Ear-vein	1498	1670	Chloroformed Nov. 11 (3 months 2 days)	
" IX.*b*	1 mo. 6 days	2d	9	0.7	40	Aug. 9, 1899 Ear-vein	1512	802	Died Sept 6 28 days)	
" IX.*c*	5 months	6th	9	0.5	43	Dec. 6, 1899 Ear-vein	1771	1794	Chlorof. Mar. 7, 1900 (3 months 1 day)	This culture (IX.*c*) was recovered from rabbit 41. The transfers are counted from the original isolation, the rabbit being counted as one.
" IX.*c*	5 months	6th	9	0.5	44	Dec. 6, 1899 Ear-vein	1977	1921	Chlorof. Feb. 12, 1900 (2 months 6 days)	
Human X. (lung tissue)	20 days	1st	20	0.5	115	Mar. 7, 1902 Ear-vein	1955	1895	Chlorof. May 9, 1902 (2 months 2 days)	Horse serum culture used in place of customary dog serum.
" "	20 days	1st	20	0.5	116	Mar. 7, 1902 Subcutis	1626	1678	Chlorof. May 28, 1902 (2 months 21 days)	Horse serum used.
" "	4 mos. 15 days	4th	13	0.5	137	June 30, 1902 Ear-vein	1650	1952	Chlorof. Aug. 29, 1902 (2 months)	
Human XI.*a* (mesenteric lymph nodes)	2 mos. 10 days	2d	18	0.5	118	May 13, 1902 Ear-vein	1675	.....	Died May 31 (18 days)	
" "	3 mos. 18 days	4th	10	0.5	120	June 21, 1902 Ear-vein	1553	1145	Chloroformed July 12 (22 days)	Would have died in one or two days.
" "	3 mos. 18 days	4th	10	0.5	89	June 21, 1902 Ear-vein	2615	2061	Died July 12 (22 days)	
" "	3 mos. 18 days	4th	10	0.5	131	June 21, 1902 Subcutis	1755	1823	Chlorof. Aug. 18 (1 month 28 days)	Extensive tuberculosis of lungs.
Human XI.*b*	4 mos. 28 days	5th	27	0.5	136	Sept. 11, 1902 Ear-vein	1920	1377	Chlorof. Oct. 7 (26 days)	Severe dyspnea; would have probably died in one or two days.
" "	4 mos. 28 days	5th	27	0.5	144	Sept. 11, 1902 Ear-vein	1895	1450	Chlorof. Oct. 3 (22 days)	Nearly dead when chloroformed.
" "	4 mos. 28 days	5th	27	0.5	155	Sept. 11, 1902 Subcutis	1735	1690	Chlorof. Nov. 19 (2 months 8 days)	Extensive tuberculosis of lungs.
Human XII. (mesenteric lymph nodes)	1 mo. 4 days	2d	11	0.5	122	May 13, 1902 Ear-vein	1453	1565	Chlorof. Aug. 18 (3 months 5 days)	Horse serum culture used.
	1 mo. 4 days	2d	11	0.5	132	May 13, 1902 Ear-vein	1680	1772	Chlorof. Aug. 18 (3 months 5 days)	Dog serum culture used as usual.
" "	5 mos. 15 days	7th	14	0.5	135	Sept. 24, 1902 Ear-vein	1957	1948	Chlorof. Dec. 18 (2 months 24 days	Horse serum culture used.

TABLE I.—*Continued.*

Designation of culture.	Total age of culture.	Number of transfer.	Age of culture used in days.	Dose in c.c.	Number of rabbit.	Date and mode of inoculation.	Initial weight, grams.	Final weight, grams.	Result.	Remarks. (For brief description of lesions, see notes under each culture, pp. 111–123.)
Bovine VIII.	3 mos. 25 days	3d	7	0.5	47	Nov. 18, 1899 Ear-vein	1345	.....	Died Dec. 2 (14 days)	
" "	3 mos. 25 days	3d	7	0.1	55	Nov. 18, 1899 Ear-vein	1384	1095	Chlorof. Dec. 13 (25 days)	Would probably have died in 24 hours.
" "	2 years 4 mo.	24th	8	0.5	99	Nov. 13, 1901 Ear-vein	1828	1345	Died Dec. 5 (22 days)	
Cat II.	1 mo. 21 days	1st	51	0.5	68	June 4, 1900 Ear-vein	2121	.....	Died June 22 (18 days)	
" "	1 mo. 21 days	2d	9	0.5	67	June 4, 1900 Ear-vein	2206	.....	Died June 25 (21 days)	
Cat III.	1 mo. 26 days	3d	13	0.5	77	May 31, 1901 Ear-vein	1888	.....	Died June 22 (22 days)	Animal anesthetized with chloroform before injection of culture.
" "	1 mo. 26 days	3d	13	0.5	74	May 31, 1901 Ear-vein	1980	.....	Died June 25 (25 days)	Animal anesthetized with chloroform before injection of culture.
" "	7 mos. 6 days	7th	8	0.5	85	Nov. 13, 1901 Ear-vein	2596	.....	Died Nov. 30 (17 days)	No recognizable lung lesions.
" "	8 mos. 10 days	8th	10	0.5	109	Dec. 17, 1901 Ear-vein	1850	1510	Chlorof. Jan. 14, 1902 (28 days)	Dyspnea. Disease complicated with rabbit septicemia or "snuffles."
" "	1 year 3 mos.	15th	13	0.5	145	June 30, 1901 Ear-vein	1590	1883	Chlorof. Aug. 29 (2 months)	
Dog I.a	1 mo. 7 days	2d	14	0.5	36	June 8, 1899 Ear-vein	1767	1935	Chlorof. Sept. 9 (3 months)	
" I.b	1 mo. 5 days	2d	13	0.5	37	June 6, 1899 Ear-vein	1861	1943	Chlorof. Sept. 11 (2 months 5 days)	

TABLE II.—Showing the result of the inoculation of guinea-pigs with the various tubercle bacilli in pure culture. (In all but one case the injection is intra-abdominal and the dose 0.5 c.c. of a standard suspension of tubercle bacilli from cultures)

Designation of culture.	Total age of culture.	No. of transfer.	Age of culture used in days.	Date of inoculation.	Initial weight of guinea-pig (grams).	Final weight of guinea-pig (grams).	Result.	Remarks.
Sputum IX.*a*	1 mo. 18 days	3d	9	Aug. 9, 1899	287	.....	Died Aug. 20 (11 days)	
" IX.*b*	1 mo. 6 days	2d	9	" "	362	.....	" Sept. 2 (24 ")	
" IX.*c*	5 months	6th	9	Dec. 6, "	423	281	" Jan. 4 (29 ")	Culture IX.*c* recovered from rabbit 41, [which see.
Human X.	20 days	1st	20	Mar. 7, 1902	326	250	" April 1 (25 ")	
" X.	4 mos. 15 days	4th	13	June 30, "	320	335	Chlorof. Aug. 29 (2 mos.)	Would probably have died in a few days.
Human XI.*a*	2 mos. 10 days	2d	18	May 13, "	450	.....	Died May 27 (14 days)	
" XI.*a*	3 mos. 18 days	4th	10	June 21, "	495	.....	" June 30 (9 ")	
" XI.*a*	3 mos. 18 days	4th	10	" "	358	.....	" Aug. 9 (49 ")	Inoculation subcutaneous.
Human XII.	1 mo. 4 days	2d	11	May 13, "	345	.....	" June 30 (48 ")	Dog serum culture used.
" XII.	1 mo. 4 days	2d	11	" "	356	.....	" June 20 (38 ")	Horse serum culture used.
" XII.	5 mos. 15 days	7th	14	Sept. 24, "	480	298	" Nov. 4 (41 ")	
Bovine VIII.	3 mos. 25 days	3d	7	Nov. 18, 1899	336	.....	" Nov. 28 (10 ")	
" VIII.	2 yrs. 4 mos.	24th	8	Nov. 13, 1901	470	295	" Dec. 10 (27 ")	
Cat II.	1 mo. 21 days	1st	51	June 4, 1900	761	.....	" June 12 (8 ")	
" II.	1 mo. 21 days	2d	9	" "	559	.....	" June 13 (9 ")	
Cat III.	1 mo. 26 days	3d	13	May 31, "	383	.....	" June 30 (30 ")	
" III.	4 mos. 16 days	6th	20	Aug. 21, "	469	447	Chlorof. Oct. 1 (41 ")	Animal showed but few symptoms of disease. Injection mainly subcutaneous.
" III.	1 year 3 mos.	15th	13	June 30, "	377	282	Died Aug. 21 (54 days)	
Dog I.*a*	1 mo. 7 days	2d	14	June 8, 1899	400	286	" June 20 (12 ")	
" I.*b*	1 mo. 5 days	2d	13	June 6, "	428	.....	" July 1 (25 ")	
" I.*b*	1 mo. 5 days	2d	13	" "	422	.....	" July 1 (25 ")	

TABLE III —Inoculation of cattle with human cultures XI. XII., October 18, 1902.

Designation of culture.	Total age of culture.	No. of transfer.	Age of culture used in days.	Amount injected, c.c.	Designation of animal.	Mode of inoculation.	Age and sex of animal.	Original weight (pounds).	Final weight (pounds).	Remarks.
Human XI.	7½ mos.	9th	10	2½ c.c.	7	Intra-abdominal (intramuscular?)	Black and white bull, yearling.	462½	572½	Killed December 23, 1902.
" XI.	7½ "	9th	10	2 "	9	Intrathoracic.	Dehorned black and white steer, yearling.	417½	.....	Killed, greatly emaciated and weak, Nov. 25, 1902, weight probaby reduced to one-half.
" XII.	6⅓ "	9th	10	2½ "	6	Intra-abdominal (intramuscular?)	Black and white bull, yearling.	400	530	Killed December 23, 1902.
" XII.	6⅓ "	9th	10	2 "	8	Intrathoracic.	Heifer, yearling.	490	600	Killed December 23, 1902.

In the tables (I. and II.) on pages 124–126, the various data bearing upon the inoculation of rabbits and guinea-pigs with standard suspensions of tubercle bacilli from cultures are brought together. These figures are strictly comparable with those given in former papers on this subject, and the reader is also referred to what is there stated concerning the experimental disease in these animals. In general a careful scrutiny of the tables will show that with rare exceptions the reaction of these animals toward the same culture is very uniform. The occasional divergences exclusive of secondary infections are, I believe, explainable along the following lines: In rabbits, for instance, we have three types of the experimental disease after intravenous injection, the rapidly fatal disease induced by bovine bacilli in two to three weeks, the mild disease induced by human cultures which would probably last six months or longer if the animals were allowed to live, and an intermediate type rarely seen. In the latter the rabbits succumb in four to five weeks after very great emaciation due probably to toxemia. This aberrant condition is attributable to two kinds of factors. The first are external and cause a distribution of the bacilli in the body different from that which usually takes place. In a former paper I referred to the case of a rabbit which escaped into a room immediately after inoculation and was caught only after considerable difficulty. It developed this toxic type of the disease. In the present paper the two rabbits inoculated with culture Cat III. (Nos. 74 and 77) were chloroformed before inoculation and the course of the disease was probably modified and made more severe thereby. The second class of factors are probably internal, and may operate as follows: Certain rabbits which are somewhat less resistant permit the bacilli to multiply in the body up to a certain point, when, owing to an increase in the immunity, the bacilli are attacked and a large amount of poison is liberated which induces the marked depression and emaciation. In such a case the rabbit may successfully check the progress of the disease, but lose its life in the effort. This is probably the explanation of the early death of No. 40 inoculated with human culture IX.*b*. The other rabbits, acting more promptly, destroy the greater number of bacilli injected before the latter have had time to multiply.

Guinea-pigs manifest less regularity in their resistance to experimental tuberculosis, which is due to a variety of causes. Guinea-pigs weighing less than 300 grams are quite susceptible. The same is true

of guinea-pigs weighing over 500 grams, but for other reasons. In the latter fatty degeneration is a process quite conspicuous. In the case of intra-abdominal inoculation, the disease is probably more or less modified by the particular organs primarily attacked, the number of adhesions formed, etc. Nevertheless, even with guinea-pigs differences in virulence are recognizable. This is very evident when we compare human X., XI., and XII. in the guinea-pig table. Here XI. stands out distinctly as the most pathogenic. The results of inoculations with suspensions of tuberculous tissue run parallel to those tabulated, but they are omitted because the number of bacilli introduced is variable and not measurable.[1]

Virulence Tests of Cultures Human XI. and XII. upon Cattle.

The relatively high degree of virulence possessed by culture XI. made it desirable to test it upon cattle, in order to trace its source still more definitely. All inoculation tests have a greater comparative than absolute value, owing to the method of introducing the virus, the quantity used, and the possible attenuation in virulence by artificial culture. In these respects inoculation departs from the spontaneous infection going on in nature. Bearing these facts in mind, I considered it very important to make parallel tests with culture XII. because the two had been isolated from the same kind of tissue—mesenteric lymph nodes of children—and because they were found markedly different in other respects.

Four animals were used.[2] These were between twelve and eighteen months old. All had still their first sets of incisor teeth. They were

[1] In concluding this descriptive chapter on these cultures, the question may be raised as to the best method of bringing out the comparative virulence of cultures in rabbits and guinea-pigs. The method of intravenous injection in rabbits was chosen in preference to the subcutaneous because it gives results more promptly and because there is no likelihood of the virus being scattered and endangering attendants except through the urine after three or four months. In rabbits subcutaneous inoculation gives rise to large abscesses which may break; the same criticism would apply to the subcutaneous inoculation of guinea-pigs. Intraocular inoculation was not used because results are as satisfactory with methods less painful and annoying to the animal. For special purposes various methods must be used, but the above are very useful and safest for long series of comparative tests.

[2] These were kindly furnished by the Cattle Bureau of the Department of Agriculture of Massachusetts through its chief, Dr. Austin Peters, in view of the practical bearing of such tests upon the dairy industry. I am also indebted to this Bureau for attendance and food of the animals while under observation.

very vigorous animals, and free from tuberculosis, as shown by a tuberculin test. Every effort was made to have the conditions respecting the two cultures to be used as uniform as possible. Both were kept on dog serum and were used when they were ten days old. Owing to the feeble multiplication of XI., the suspension in sterile bouillon was made by pouring the latter into the culture tube and stirring it about. The fluid, not having reached a sufficient density, was removed from this tube and poured into a second culture on horse serum of the same age. The resulting suspension contained many fine granules and it was allowed to subside for half an hour, when the cloudiness corresponded closely to the adopted standard. A hand lens, however, still revealed very fine granules in it. The culture of No. XII. was quite fair on the tenth day, and from it portions were removed with platinum wire, rubbed on the inside of a dry, sterile test tube, and then bouillon poured in until the suspension assumed the desired density. It also contained many very fine granules. Two animals were inoculated with each culture, one of each pair into the thorax, the other into the abdomen. The inoculations into the thorax were made in the same way as in former experiments. The needle of the syringe, two inches long, was thrust through the chest wall on the right side, between the seventh and eighth ribs and about ten inches above the level of the elbow, and 2 c.c. injected. The inoculation into the abdomen was made by thrusting the needle through the wall on the right side, just below the triangular depression in front of the iliac spine, and $2\frac{1}{2}$ c.c. injected.

These doses are considerably smaller than those employed by other experimenters recently; but they are the same as used by me in former tests on cattle.

At the same time two guinea-pigs were inoculated intraperitoneally with 0.5 c.c. of the same suspensions to make sure that the cultures were active. The guinea-pig which received culture XI. died in thirteen days, the one which received culture XII. in twenty-two days. In both animals the lesions were typical of tuberculosis.

Of these four animals No. 9, the steer inoculated intrathoracically with culture XI., soon showed signs of disease. The temperature began to rise at once and reached 105° F. and above. It remained above 105° for about two weeks, touching once at 107.3°. During the following two weeks it gradually fell to 104°. In the meantime the

animal began to grow thin, the respiratory movements became somewhat labored. In the fourth week he became very weak and thin and lay much of the time. Diarrhea also appeared. It was now thought best to kill the animal, and on November 25th, thirty-eight days after inoculation, this was done. The following details taken from the autopsy notes indicate the nature of the disease (see temperature curves on pages 131 and 143 and Table III. on page 126):

Subcutaneous lymph glands not affected.

Thorax. General adhesion of right lung to chest wall and to corresponding portion of diaphragm. After removal of the organs *en masse* the following points were noted:

The left lung is permeated with crowded, translucent tubercles ½ mm. and less in diameter. No other changes in this lung, excepting scant adhesions of the margin of cephalic lobe to surrounding structures.

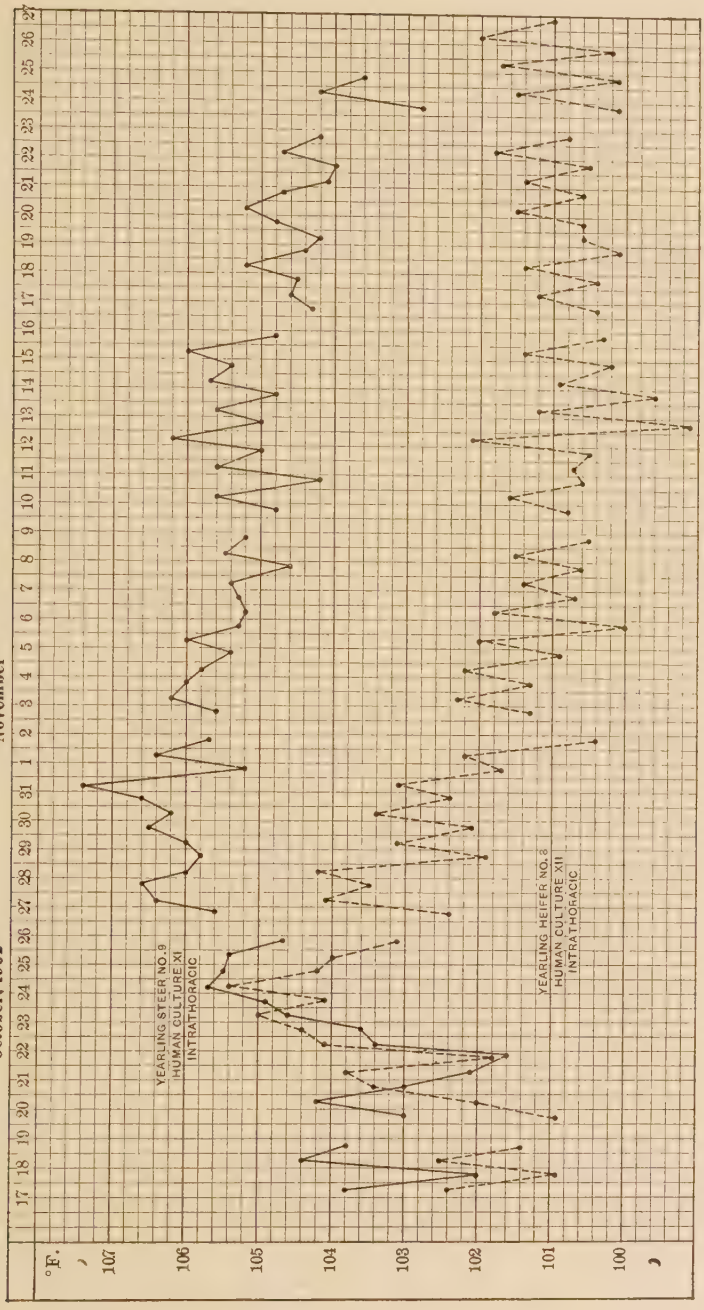
The right lung is largely concealed and compressed by a large oval mass of yellowish, firm tissue. When incised the heart is found within it, encased in neoplastic tissue varying from two to six inches in thickness. It is composed of the greatly enlarged tuberculous lymph nodes of the anterior mediastinum, bound together by tuberculous infiltration of the pleura, pericardium, and connective tissue of the anterior mediastinum. The immediate site of the inoculation in this mass is occupied by a tuberculous focus three to four inches in diameter, on section grayish in color and permeated with a dense network of yellowish lines in which gritty particles can be detected. The entire neoplasm suggests closely the appearance presented by tissue of bovine tuberculosis in a state of rapid proliferation. The left half of the pericardium is but slightly thickened and beset over an area 2 to 3 inches in diameter with coalescing tubercles about 2 mm. diameter, forming flattened, sessile patches. The inner surface of the pericardium is free from tubercles, but on the epicardium at the base and at the roots of the large vessels are agglomerations of tubercles probably ½ mm. diameter, having a bright pink color, and forming irregular patches.

The dorsal mediastinal lymph nodes are all two to three times the normal size. The cut surface appears as a grayish matrix, penetrated with a dense, fine, yellowish network. The lymph nodes in the ventral mediastinum near the first rib are in a similar condition. The right lung, greatly compressed by the new tissue above described, is of a red color, edematous, and permeated with tubercles, like those in the left lung.

The organs in the abdominal cavity were normal in appearance. Macroscopically tubercles were not recognized. There were a few scattering nodules on the omentum of doubtful nature, and in the liver minute, gray-yellow points of hazy outline about 1 mm. diameter appeared near the surface.

Of this animal the lung tissue, the excrescences in the pericardial sac, one of the mediastinal glands, the liver and the spleen were examined micro-

CHART 1.


October, 1902
November
°F.
107
106
105
104
103
102
101
100
YEARLING STEER NO. 9
HUMAN CULTURE XI
INTRATHORACIC
YEARLING HEIFER NO. 8
HUMAN CULTURE XII
INTRATHORACIC

scopically. The lesions in the lungs consisted of small, isolated tubercles, the largest about ½ mm. in diameter. They were situated chiefly in the respiratory portion of the lung tissue. Only a few were peribronchial. The structure of the tubercles was similar to that encountered in spontaneous cases, but giant cells were absent. There was also more necrosis than in such cases. The tubercle bacilli were very numerous, but with few exceptions they stained feebly and were rather thin, slender, and some more or less fragmented.

The tubercles occurring as dense, plaque-like outgrowths of the epicardium resembled closely those of the lung tissue as regards necrosis, absence of giant cells and many bacilli. Contrary to tubercular outgrowths in spontaneous cases, there was here much proliferation of cells and formation of blood-vessels. The new tissue formed a kind of matrix within which the tubercles were situated.

In the mediastinal gland the chief feature was extensive necrosis, the necrotic tissue having a hyaline appearance. Nuclear debris was quite scarce in it. Bacilli were detected in considerable numbers.

In the spleen tubercles were found in small numbers, occupying the Malpighian bodies. Here the structure was more like the tubercle in spontaneous cases. It consisted of epithelioid cells forming an indistinctly fused mass in which a few small, compact nuclei were scattered. Giant cells were present, and a moderate number of bacilli. The tubercles in the liver were like those in the spleen. They were situated either in the portal area or within the lobule. The largest were about ¼ mm. in diameter.

It would seem that in this case the disease expended its chief energy in the thorax, where the tubercle bacilli were deposited, producing there a large, tumor-like mass, involving the anterior mediastinum and the pericardium. The sections revealed a generalized tuberculosis with submiliary tubercles in spleen and liver.

The yearling heifer, inoculated in the same manner as the preceding, but with culture XII., manifested nothing unusual during the entire period under observation (nine weeks) excepting a high temperature, which started in two days after inoculation, reached its acme of 105.4° on the sixth day, and then rapidly fell again, reaching the normal level on or about the eighteenth day, and remaining normal thereafter. The animal had gained in eight weeks one hundred and ten pounds. On December 23d she was killed.

The only indications of the injection of tubercle bacilli were, on the right side, lines of delicate, injected, connective tissue fringes along the margins of the ribs. Similar delicate fringes springing from the pulmonary pleura along the lines of the interlobular septa of the convex surface of the right lung. On the lateral margin of the main

(caudal) lobe two firm nodules, pea-size, centrally necrotic. The thoracic lymph nodes free from tuberculous lesions. Abdominal organs normal. Two fetuses, about two feet long, in utero.

In this animal there were no lesions produced in the thorax beyond what might have been expected of a dose of dead tubercle bacilli. Yet the temperature curve suggests a transient multiplication.

On page 131 the temperature curves of both animals are placed side by side, that of XI. until the animal was killed, that of XII. only in part, the omitted portion being normal.

The two animals which were inoculated into the abdomen did not show signs of disease beyond a period of high temperature. This was explained by the fact noted at the autopsies, that the fluid was largely deposited in the subcutaneous and intramuscular tissue of the abdominal wall.

No. 7, inoculated with culture XI., developed a febrile temperature from two to three days after inoculation. The highest point reached was 104° on the fourth day. It touched 103° and above until the seventeenth day, when it fell below 102°. After the first month it remained below 101°, with the exception of one day. The animal gained one hundred and ten pounds in eight weeks. It was killed November 23. The only lesions noticed were the following:

At the point of inoculation there were two roundish masses in the subcutis made up of a thin, cyst-like wall, and completely softened, yellowish, cheesy contents. In the intermuscular tissue and producing a slight bulging of the abdominal wall into the peritoneal cavity was a firm, roundish mass about two inches across. On section it was found to consist of a central, necrotic, and slightly calcareous mass of irregular outline, enveloped in a dense, pearly white capsule. The whole was embedded in muscular tissue. No indication of any local spreading of the process, but in the lymph node of the right knee-fold a necrotic focus about 1 cm. diameter and of the same character as the lesion described. The axillary node of the same side normal. There was no indication that the bacilli had entered the peritoneal cavity.

In No. 6, inoculated in the same way as No. 7, but with culture No. XII., a febrile temperature appeared within two to three days reaching its acme of 104.4° on the sixth day, and then slowly declining to normal, which it touched on the twenty-first day. A slight second rise was observed, reaching its acme of 103° on the twenty-seventh day.

From this date it slowly descended and remained normal until the animal was killed. In this animal the daily oscillations were quite pronounced, amounting to 2°. These oscillations continued in part through the normal period. The gain in weight in eight weeks was one hundred and thirty pounds. When killed, November 23, the following lesions were noted:

In the subcutis, corresponding to the point of inoculation, two sacs, one-quarter and one-half inch in diameter, filled with uniformly softened, cheesy matter. In the deeper muscular tissue at the same site is another focus consisting of an agglomeration of nodules up to one-half inch diameter. The entire mass flattish, about one inch in diameter. The individual tubercles are yellowish, cheesy. No lesions of the subcutaneous lymph node in the knee-fold. On the omentum over the rumen are scattering discolorations barely visible except in a certain light. They are probably the result of slight hyperplasia of the omentum. On the diaphragm two pea-sized and several very small, roundish bodies, provided with a short, constricted pedicle.

These were examined in sections from tissue hardened in Zenker's fluid and embedded in paraffin. They consisted of masses of fusiform connective tissue cells, richly supplied with bloodvessels. No trace of tubercles or necrotic tissue was seen, although the sections passed nearly through the centre of the nodule.

It is highly probable that in this case the bacilli entered the peritoneal cavity, as indicated by the neoplasms on the diaphragm and perhaps the faint spots on the omentum. This would explain the slightly greater febrile reaction of this case as contrasted with No. 7, which received bacilli of so much higher pathogenic power, but which failed to enter the abdomen. The result is not surprising, therefore, since the subcutaneous and muscular tissues present more or less resistance to the virus of tuberculosis.

Setting aside as of uncertain value these two abdominal inoculations, we have the two intrathoracic inoculations upon which to base our estimate of the relative virulence of cultures XI. and XII. There is no uncertainty as to the capacity of XI. to produce genuine tuberculous lesions in cattle, while XII. was practically harmless. It is not to be denied that the pathogenic power of XI. appeared to be somewhat below that of cultures from cattle; but this difference is not of sufficient magnitude to place the culture outside the bovine race of tubercle bacilli, especially when we take into consideration the temporary sojourn of XI. in the human subject and the possibility of slight modification therein.

The Influence of Passages of Tubercle Bacilli through a Series of Rabbits upon Their Biologic Characters and Virulence.

The isolation of only a certain race of bacilli from the pulmonary forms of human tuberculosis, which race differs in important features from the bovine race, naturally raises the question of a transformation of the bovine into the human type in the human body. This possibility was acknowledged by me in 1898 as worthy of consideration, and I assumed that if such transformation does occur the infection probably begins in the mesenteric glands, and sooner or later appears in the lungs.[1] It is wellnigh impossible to approach the subject satisfactorily from the experimental standpoint, owing to inherent difficulties. Attempts have been made by Vagedes and Ravenel. Vagedes[2] passed a highly virulent culture of human origin through twelve rabbits without observing any shortening of the period of disease. Another culture appeared to him to have increased in virulence after four passages. The comparative test made with this and the original culture is not convincing, however, for both rabbits of the passage virus died of intercurrent disease. An attempt to increase the virulence of a human culture by passages through rats promised more success; but the series could not be continued.

Ravenel[3] passed a human culture isolated from sputum through five calves. The first calf was inoculated first in September, 1901, and repeatedly thereafter until 925 c.c. of culture suspension had been injected. On the death of this animal December, 1901, a second calf was inoculated with an emulsion of the bronchial gland of the first calf both into the lungs and the abdominal cavity. The third calf was inoculated with an emulsion made from the tubercles of the omentum of the second calf, and so on.

The jump in pathogenic power in this series is very marked after the first case and indicates a decided change in the activity of this bacillus. An experiment of this kind, involving a matter of such practical moment, must, however, be dealt with critically. I am not prepared to accept this single experiment as establishing the possi-

[1] Journal of Experimental Medicine, 1898, iii. p. 451.
[2] Zeitschrift f. Hygiene, 1898, xxviii. p. 276.
[3] University of Pennsylvania Medical Bulletin, May, 1902.

bility of an increase in virulence of the human variety of bacilli in cattle. In spite of all precautions errors may creep in when a species eminently susceptible to the bovine bacillus is used, when the experiment extends over such a long period and so much culture fluid is injected that freedom from errors can only be established by several concordant results. On the other hand, it is conceivable that in such an experiment indicating sudden increase in virulence the culture used may have been originally a bovine culture grafted upon the human subject and thereby attenuated. Such a culture would probably respond quickly to serial inoculations, whereas a true human type may not.

Since 1898 I have endeavored to attack the problem in the only way open to me by passing cultures through a series of rabbits, the object being to see if any modification whatever could be brought about. The method consisted briefly in inoculating a certain animal, chloroforming it after a time and recovering the culture for injection into another animal. Theoretically it would have been better to have injected the tuberculous tissue of each animal into the following instead of endeavoring to recover and use a culture each time, since it may occur that the more virulent bacilli, growing less easily on artificial media, may be suppressed each time in the culture in favor of the more saprophytic individuals. However this may be, the inoculation with tuberculous tissue is apt to fail sooner or later, owing to the few bacilli present and the high degree of resistance offered by rabbits. The rabbit was chosen because it was assumed that an animal resistant to any micro-organism would be more likely to modify it than one highly susceptible to it.

Table IV. epitomizes what was done upon this phase of the problem. At first a human culture was used to see if any increase in virulence might take place in the rabbit. After the bacillus had been passed through four rabbits it became evident that it was growing less instead of more virulent. The bacillus during this experiment was in contact with the living tissue of three rabbits for fifteen and one-sixth months and in cultures in the intervals four and five-sixth months. Though the fourth rabbit received a large intravenous dose it gained over 300 grams in one and one-half months. In fact, the effect upon the third rabbit had already indicated attenuation rather than increase in virulence. The experiment was therefore not continued any further in this direction.

TABLE IV.—Passage of human and bovine bacilli through a series of rabbits.

Number of animal.	Period of cultivation since preceding inoculation.	Age of culture used.	Date of inoculation.	Mode of inoculation.	Dose in c.c. of standard suspension.	Initial weight.	Final weight.	Remarks.
				Human (sputum) III.				
45	1 year 13 days	16 days	Mar. 1, 1898	Ear-vein	1.0 c.c.	1707	1520	Sept. 1, 1898. Tuberculosis of iris; chloroformed; foci in kidneys, with discharge; scattering foci 2–3 mm. in lungs.
28	1 mo. 5 days	11 "	Oct. 5, "	"	0.5 "	2338	1949	Feb. 20, 1899. Tuberculosis of iris; chloroformed; one focus 3 x 10 mm. in lungs; foci in kidneys, with discharge into urine.
22	1 month	14 "	Mar. 20, 1899	"	1.0 "	1640	1863	Aug. 11, 1899. Chloroformed; three small foci in lungs, several in kidney; bacilli in pelvis of one kidney.
34	1 mo. 18 days	11 "	Sept. 29, "	"	1.0 "	1340	1660	Nov. 15. Has gained over 300 grams, in six weeks used for other experiments. Chloroformed April 14, 1900; one large softened focus in lungs, and some large ones in kidney extending into pelvis.
				Bovine VIII.				
55	3 mos. 25 days	7 days	Nov. 18, 1899	Ear-vein	0.1 c.c.	1353	1095	Dec. 13, 1899. Chloroformed; marked dyspnea, extensive miliary tuberculosis of lungs, liver, and spleen.
54	1 month (2 transfers)	10 "	Jan. 13, 1900	Abdomen	0.05 "	1828	1702	March 26, 1900. Chloroformed; extensive eruption of tubercles in abdomen; lungs permeated with many groups of coalescing tubercles.
52	28 days	28 "	Apr. 23, "	"	0.05 "	1958	.....	June 18, 1900. Died; extensive eruption of tubercles on peritoneum; dense eruption of tubercles in lungs.
65	3 mos. 18 days (4 transfers)	9 "	Oct. 6, "	Ear-vein	0.04 "	1530	.....	Nov. 8, 1900. Chloroformed; many tubercles in lungs, some in kidneys.
71	1 mo. 13 days (2 transfers)	10 "	Dec. 21, "	Abdomen	0.025"	2050	.....	Jan. 19, 1901. Dyspnea; chloroformed; extensive eruption of tubercles in abdomen and lungs.
75	4 mos. 12 days (5 transfers)	13 "	May 31, 1901	"	0.01 "	2210	1660	July 5, 1901. Dyspnea; chloroformed; extensive eruption of tubercles on peritoneum and in lungs.
81	1 mo. 16 days (2 transfers)	20 "	Aug. 21, "	Ear-vein	0.01 "	1665	1280	Sept. 29, 1901. Chloroformed; scattering tubercles in lungs.
97	1 mo. 15 days (2 transfers)	8 "	Nov. 13, "	"	0.5 "	1842	1265	Dec. 4, 1901. Died; extensive eruption of tubercles in lungs and spleen.
99 (control)	2 years 4 mos. (24 transfers)	8 "	Nov. 13, "	"	0.5 "	1828	1345	Dec. 5, 1901. Extensive eruption of tubercles in lungs.

A bovine culture was next tried. This experiment extended over a period of two years, with gaps of considerable length intervening between some of the series. This was due to various causes, the chief being the difficulty of obtaining satisfactory cultures each time. The culture was, however, recovered six times. Another difficulty was the appearance of pneumonia in certain inoculated animals due to the latent presence of the rabbit-septicemia bacillus in the upper air passages. The disease appeared only when the lungs had been weakened by the tuberculous infection.

The exact influence of the passage through the seven rabbits does not appear clearly. The eighth rabbit succumbed at nearly the same time with the control rabbit, which received the same dose of the culture not passed through rabbits. There was thus not enough difference between the two cultures (the one that was passed through rabbits and the other that was not) to warrant any inference as to the probable effect of a much longer series of passages, and we can only state that the bovine bacillus is tenacious of its virulence for years as manifested toward rabbits, while the human bacillus experimented with probably lost in virulence in its contact with the tissues of the rabbit.

The figures given in Table IV. are, however, not wholly without value. We have there a very plain demonstration of the striking difference in the virulence of the bovine as compared with the human type of tubercle bacilli. An examination of the column marked "dose in c.c." shows that 0.01 c.c. of bovine VIII. is still far more virulent than 1 c.c. of sputum III.

While the pathogenic power of the bovine culture did not appear to be appreciably changed with respect to rabbits, the culture itself underwent modification, as compared with the original culture, in two directions.

1. The cultivation of the passage bacillus was much more difficult and the resulting growth quite feeble in comparison with the original, so that it required great care to recover and maintain it after each rabbit of the series. In other words, the passage culture had reverted in a certain degree to the culture soon after isolation from the cow. Perhaps the more saprophytic individuals were destroyed each time in the inoculated rabbit, leaving only the less easily cultivated individuals to be transferred to culture tubes. That there is, other things

being equal, an inverse relation between virulence and rapidity and abundance of growth in culture media is especially conspicuous among the tubercle bacilli.

2. The bacilli of the passage culture appeared in stained preparation in the forms usually seen after recent isolation—*i.e.*, short, often tapering slightly from one end to the other and somewhat polymorphic. Those of the original culture assumed the peculiar forms closely resembling spore-bearing bacilli with the spores stained. A deeply stained, short, plump, rod-like mass was continued at either end by a feebly stained, barely visible prolongation, suggesting the disintegrating body of a spore-bearing bacillus. These peculiar forms will be described and figured in another paper. They are the result of prolonged artificial cultivation.

A Simple Method for Distinguishing the Bovine from the Human Type of Bacilli in Bouillon Cultures.

The microscopic study of tubercle bacilli has not yielded any diagnostic features of value, excepting the short, plump form, which should arouse our attention when encountered in serum cultures from the human subject and stimulate to further tests, among which the inoculation of rabbits has proved of the greatest value to me. Additional characters are therefore desirable, and the following cultural differences added to those above bid fair to enable us to recognize bovine bacilli.

When flasks of glycerin bouillon in layers $1\frac{1}{2}$ to $2\frac{1}{2}$ c.m. deep are inoculated with scales of tubercle bacilli from glycerin-agar cultures the floating masses soon begin to expand, and after one or two months a complete membrane will have formed over the relatively clear bouillon. The bacillar masses which fall to the bottom at the outset increase but slightly in size. This mode of surface growth of tubercle bacilli was shared by all mammalian races I have examined after they had acquired a certain saprophytic habit, and it is well known to all those who cultivate tubercle bacilli for the preparation of tuberculin. If ordinary bouillon prepared from fresh beef with 3 to 5 per cent. glycerin added be used, and if the acidity be made equivalent to about 2 per cent. of normal acid, phenolphthalein being the indicator, the reaction of the bouillon during the formation of the membrane

will take one of two directions. It may gradually approach the neutral point and reach an acidity or an alkalinity of about 0.1 to 0.2 per cent. when the membrane is complete and remains so, or else the acidity may diminish during the first month, to increase again during the second and fluctuate more or less if the observation be continued, but it does not reach the neutral point. These movements of the reaction curve are given in Table V., where the cultures tested are grouped according to the bouillon used.

An inspection of this table will reveal the curious fact that all the cultures derived from animals (excepting *Nasua*) and one human culture (XI.) more or less rapidly approach the phenolphthalein neutral point. The greater number go beyond this point and maintain a feebly alkaline reaction. When the growth is feeble as with human XI., and when perhaps the supply of air is restricted, the culture fluid does not always reach the neutral point, but may remain 0.1 to 0.2 per cent. acid. In the human cultures, on the other hand, excluding XI., the reaction curve also moves toward the neutral point, but soon swings back to a greater acidity. The culture designated *Nasua*, which groups itself with the human cultures, when first isolated and studied by me was diagnosed as a human culture not only from the history of the animal and its exposure to human tuberculosis, but from the morphologic and biologic characters of the bacillus itself. This new test thus confirms a view published in 1896.

The other exception is equally interesting. Human XI., according to its morphologic, cultural, and pathogenic characters, must be classed as a bovine bacillus. By ranging itself among the bacilli, whose cultures approach and may attain a permanently alkaline reaction after three or more weeks, this bacillus is most strongly entrenched on the bovine side.[1]

It will be noticed that the age of the culture does not modify the grouping. Bovine bacilli respectively eight, five, and two years under cultivation react alike; so do human cultures five years, four years, and two months old. The *Nasua* and the culture Bovine I. have been nine years under cultivation, but their reaction curves remain

[1] Cultures U and BB received from Dr. M. P. Ravenel are also included in the table. Both are from the human subject, but BB agrees with my human XI. in having the bovine reaction curve.

TABLE V.—Reaction curves of tubercle bacilli in glycerin bouillon.

Bouillon used and composition.	Designation of culture.	Date of inoculation of the bouillon.	Reaction after (+ = alkaline, — = acid.)
No. 881. 1 per cent. Witte peptone, 5 per cent. glycerin (by volume); reaction = — 1.8	Sputum VI.	Nov. 20, 1901	42 days = — 1.8
	" "	" " "	" " = — 1.8
	Bovine VIII.	" " "	" " = + 0.1
	" "	" " "	" " = + 0.1
No. 919. Prepared same as 881; reaction = — 2	Sputum VI.	Feb. 2, 1902	33 days = — 0.55; 47 days = — 1.15
	Bovine VIII.	" " "	" " = + 0.0; " " = + 0.1
	Cat III.	" " "	" " = + 0.05; " " = + 0.1
	Horse I.	" " "	" " = + 0.0; " " = + 0.15
	Bovine III.	" 9, "	43 " = + 0.05
No. 933. Prepared same as 881; reaction = — 2.05	Sputum VI.	Mar. 5 1902	34 days = — 0.55; 48 days = — 1.15
	Nasua	" " "	" " = — 1.0
	Bovine I.	" " "	" " = + 0.05; 48 days = + 0.1
	" III.	" " "	" " = + 0.1
	" VIII.	" " "	" " = + 0.1; 47 days = + 0.15
No. 946. Prepared same as 881; reaction = — 2	Human X.	April 7, 1902	60 days = — 0.7
	" "	" 23, "	55 " = — 0.8; 78 days = — 1.4;
			94 " = — 1.35
	" "	" " "	55 " = — 0.9; 78 days = — 1.4;
			94 " = — 1.35
	Nasua	" " "	22 " = — 0.65; 31 days = — 0.9;
			51 " = — 0.35; 78 " = — 0.6
	"	" " "	38 " = — 0.7; 61 " = — 0.35;
			78 " = — 0.5
No. 996. Prepared same as 881; reaction = — 1.9	Human XII.	June 21, 1902	54 days = — 0.7
No. 1008. Prepared same as 881; reaction = —2. Trace of muscle sugar only.	Bov. VIII.*a*	Aug. 14, 1902	22 days = + 0.1 (this culture had been passed through 7 rabbits. See text, p. 135).
No. 1039. Same as 881, excepting 3 per cent. glycerin. Small amount of muscle sugar; reaction = — 1.4	Sputum VI.	Oct. 8, 1902	52 days = — 0.9; 75 days = — 0.85;
			99 " = — 1.25
	Human XI.	Nov. 7, "	60 " = — 0.2 (thin membrane covering about ¾ of surface only).
	Bovine I.	Oct. 9, "	32 days = — 0.2; 58 days = + 0.15
	" III.	" 8, "	26 " = + 0.1; 45 " = + 0.1
No. 1042. Fermented bouillon containing 3.5 per ct. glycerin and 2 per cent. Witte peptone. Moderate amount of muscle sugar left; reaction = — 1.3	Human XI.	Nov, 7, 1902	38 days = + 0.05 (membrane thin, but complete).
	" X.	Oct. 9, "	37 " = — 0.3; 51 days = — 0.9
	Bovine I.	" " "	37 " = + 0.05
	" III.	" " "	44 " = — 0.1; 67 days = + 0.1
No. 1050. Prepared same as 881; 3.5 per ct. glycerin; reaction = — 2. Moderate amount muscle sugar.	U. (Ravenel)	Nov. 7, 1902	38 days = — 0.8; 59 days = — 1.7
	Human XI.	" " "	45 " = — 0.25 (membrane feeble, covers only ⅔ of fluid);
			81 " = + 0.05 (membrane as before).
	" "	" 22, "	54 " = — 0.2 (membrane feeble, covers only ¾ of fluid).
	" XII.	" 7, "	38 " = — 0.85; 59 days = — 2.0
	Bovine I.	" " "	45 " = — 0.15 (contaminated subsequently.)
No. 1065. Prepared same as 881; 5 per cent. glycerin; reaction = —1.85. Muscle sugar as in 1050.	Human X.	Dec. 31, 1902	52 days = — 0.7; 77 days = — 0.7
	" "	" " "	" " = — 1.25; 77 " = — 1.0
	" "	" " "	" " = — 0.85; 77 " = — 1.0
	" XI.	" 15, "	53 " = — 0.15; 80 " = — 0.15
	" "	" 22, "	67 " = — 0.15
	Bovine VIII.	" 31, "	52 " = — 0.2
	" "	" " "	" " = — 0.35; 71 days = — 0.15
	B. B. (Ravenel)	Jan. 7, 1903	51 " = + 0.0
No. 1076. Prepared same as 881; 3 per cent. glycerin; reaction = — 2.15. Large amount of muscle sugar.	Nasua	Feb. 11, 1903	35 days = — 1.2; 52 " = — 0.85
	Cat III.	" " "	" " = — 0.05 52 " = — 0.05
	Horse I.	" " "	" " = — 0.4; 73 " = — 0.15
	Human XI.	" 6, "	40 " = — 0.05; 57 " = — 0.05
	B. B. (Ravenel)	" 27, "	35 " = — 0.05; 56 " = — 0.05

unlike one another. On the other hand, each agrees with its proper group. Similar biochemical differences between the members of other large groups of related bacteria lead me to regard the distinctions here brought out to be of fundamental importance. In the colon group the presence of some sugar, like lactose, in sufficient quantity will cause the true colon bacillus to produce a strongly acid reaction of the medium after a few days, while some pathogenic derivative, like the paracolon, icteroides, or hog-cholera bacillus, will produce an alkaline reaction after the same period. Here one culture acts upon the sugar, the other does not. Some such difference appears to exist between bovine and human tubercle bacilli. Just what it consists in must be determined by cultures in synthesized media or by analysis of the products in glycerin-bouillon cultures. In the mean time a more detailed inspection of the figures given may be of interest.[1]

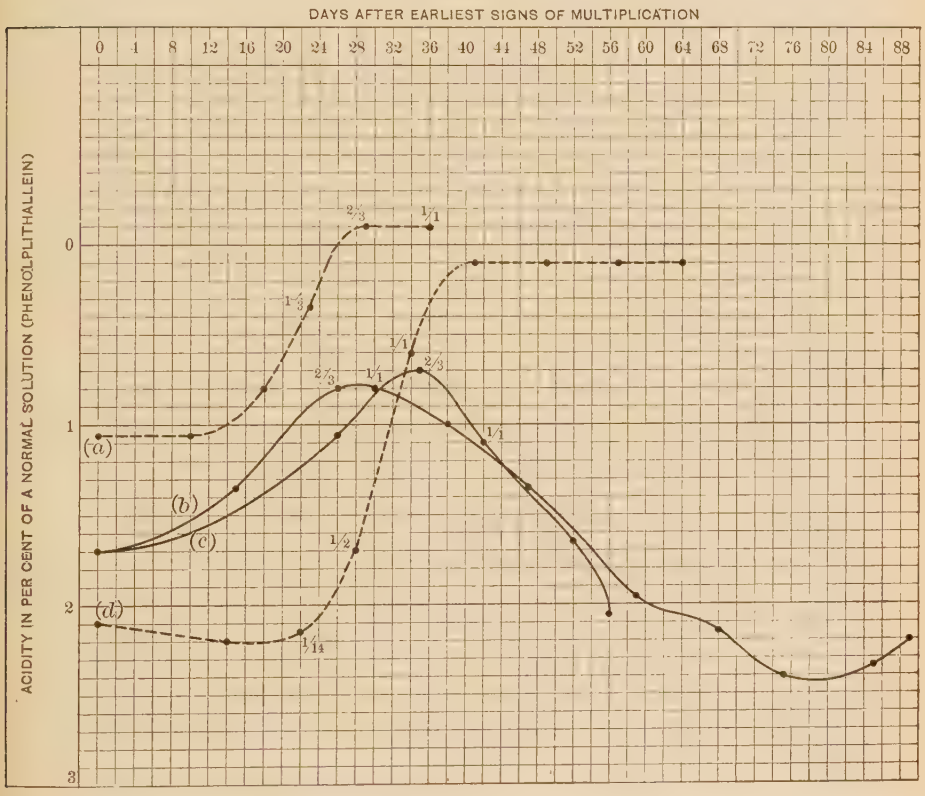
The reaction curve of the bovine cultures moves steadily from the acid to the feebly alkaline level, where it remains. The latter is reached in some lots of bouillon as early as three weeks, in others somewhat later. Very rarely it does not reach it. The reaction curve of the human cultures is more complicated. During the formation of the membrane the acidity is gradually reduced and may fall as low as 0.3 per cent. After the membrane is completed, and as it grows thicker and enlarges in all directions by pushing the margin up the sides of the flask or even down into the fluid, the acidity gradually rises again, and it may reach 2 per cent. More commonly it fluctuates between 0.5 and 1.5 per cent. In no instance have I seen any of these cultures become neutral or faintly alkaline to phenolphthalein.

It would seem as if the acid-producing group of bacilli carried on activities of two kinds. During the early growth of the bacilli the acid of the bouillon disappears in part. Later another process begins or at least predominates, which may be associated with some decom-

[1] In some experiments concluded since the completion of this manuscript I was able to obtain a fair growth of tubercle bacilli in ordinary bouillon to which no glycerin had been added. In these flasks the reaction curve was the same for human and bovine bacilli. It approached and passed slightly beyond the neutral point. Moreover, in these flasks, as well as in others containing glycerin bouillon, I was able to demonstrate by fermentative tests that the tubercle bacilli leave the fermentescible muscle sugar untouched. The evidence thus points clearly to some qualitative or quantitative difference in the action of these two groups of bacilli upon glycerin.

position of the glycerin into acids and which probably outstrips the alkaline process and masks it. The difference between the reaction curve of the bovine and the human type of bacilli is well shown by the four curves plotted in Chart 2. They were obtained by the repeated titration of glycerin bouillon in large flasks containing

CHART 2.



siphons.[1] The membrane was left undisturbed in all cases. Since some time may elapse—two to four weeks—before the transplanted bacilli show signs of multiplication, the curves are made to begin when multiplication has set in, as indicated by a slight expansion or thickening of the transferred scale of bacilli. The days on which

[1] Journal of Experimental Medicine, 1899, iv. p. 380.

fluid was drawn for titration are indicated by dots on the curves. Each time enough fluid was withdrawn into a separate tube to empty the siphon. The reaction of the fluid withdrawn after this was used for the curves. The fractions placed near the dots indicate how much of the culture fluid was covered by a membrane at the time of titration.

Curve (*a*) was obtained from bovine VIII. growing in a fermented bouillon to which 1 per cent. peptone, 0.2 per cent. dextrose, and 3 per cent. glycerin had been added.

Curve (*b*) is from human X. multiplying in ordinary peptone bouillon containing very little muscle sugar and 3 per cent. glycerin. The first part of the curve is upward like that of the bovine type, but when the membrane is nearly complete the curve changes its direction, the fluid becoming more acid.

Curve (*c*) represents sputum VI. growing in the same lot of bouillon. The reaction curve is like that of human X. After nearly three months' incubation the experiment was stopped by the appearance of fungi in the flask.

Curve (*d*) is from bovine I. growing in ordinary, unfermented bouillon containing a large amount of muscle sugar, 1 per cent. peptone, and 3 per cent. glycerin.

The tests which have yielded these curves as well as the tabulated figures were made with as many varieties of bouillon as are ordinarily encountered. All agree in the fact that the curve of the bovine type of bacilli tends only toward the alkaline level, while that of the human type tends at first toward the alkaline level and then retreats again toward a greater acidity. In the earlier experiments the tendency among bovine bacilli to reach and go slightly beyond the neutral point was manifested earlier and in a more pronounced degree than in the later tests. This may have been due to the kind of bouillon used. The distinction, however, between the two classes of bacilli remains clear in all cases and the essential characters of the reaction curves have maintained themselves for the individual cultures during the period covered by the recorded tests.

In the concentration of cultures for tuberculin a notable difference is found in the end product according to the nature of the bacillus employed. In case of bovine cultures the tuberculin is feebly alkaline if the cultures have had ample time to multiply. The tuberculin

from the human cultures is strongly acid.[1] It seems reasonable to assume that the resulting tuberculins cannot be identical when the extraction and concentration have taken place in media of such different reaction. At the same time the toxin or specific substance may not be affected at all.

In examining cultures with this new method we must observe certain precautions, or at least adhere to certain uniform procedures in order to obtain comparable results. I would suggest the following details: The bouillon should not be fermented. It is made up with 1 per cent. Witte peptone and the acidity so calculated that it will be near 2 per cent. when the bouillon is finished. This is usually accomplished by neutralizing to 1.5 or 1.6 per cent. after the peptone and salt have been added to the boiled and filtered beef infusion. The glycerin, 3 to 5 per cent., is added before the final autoclaving. The acidity need not be as high as 2 per cent. to insure the success of the test, as the table shows.

The glycerin bouillon is autoclaved in flasks (Erlenmeyer or Fernbach) in layers 2 cm. to 3 cm. deep. In the summer months when the atmospheric moisture is high it is well to place sterilized tinfoil over the plugs before autoclaving and to renew them (from a sterile lot) each time the flask is opened for titration and replaced. I have lost many flasks on account of the penetration of fungi through the cotton-wool plug during the excessively moist summer of 1902. After three or four weeks' incubation fungi appeared within the flasks unless carefully guarded. In the winter there is little or no danger, since the dry air of the laboratory affects that of the incubator.

The flasks need not be opened and titrated until the membrane formed by the tubercle bacilli has covered the bouillon completely. Thereafter it may be tested every two or three weeks as long as the skill of the observer is able to keep the flask free from infection with

[1] The following reactions of different lots of tuberculin recently prepared illustrate these statements:

Tuberculin from culture sputum VI. requires 20 per cent. of normal alkali solution to bring it to the phenolphthalein neutral point.

Tuberculin from culture human X. requires 17.25 per cent. of normal alkali solution to bring it to the phenolphthalein neutral point.

Tuberculin from cultures of two human bacilli mixed requires 11.25 per cent. of normal alkali solution to bring it to the phenolphthalein neutral point.

Tuberculin from cultures of bovine bacilli mixed requires 0.75 per cent. of normal acid solution to bring it to the phenolphthalein neutral point.

fungi, etc. In any important test two or three flasks should be prepared at the same time. Unfortunately this test can be applied only to tubercle bacilli which have been sufficiently saprophytized to grow in glycerin bouillon. Bovine cultures require more or less time. The human culture XI. required four or five months before it would grow, and even one year after isolation the membrane formed by it on bouillon was very delicate, lace-like, and but one-third to one-fourth the bulk of that of the other bacilli.

In all cases well-known bovine and human types of tubercle bacilli should be inoculated parallel with any new culture to be grouped, and the test should not be limited to one lot of bouillon unless the result is clear and decisive. Whenever the appearance of the cultures suggests contamination of any kind and extraneous bacteria are found the reaction curve may have been modified by such contamination, for many bacteria in the presence of glycerin, especially B. coli and its associates, produce an acid in bouillon. In the case of abnormal curves this possibility must be kept in mind. The method of titration is the same as that generally employed. Five c.c. of the culture fluid in 45 c.c. distilled water are brought to ebullition and then $\frac{n}{20}$ solution of NaHO is added until a feebly pink coloration appears.

Further studies upon this particular phase of the subject with variously modified culture fluids are now in progress.

Interpretation of Results.

The foregoing experimental data may be considered under two heads: the relation of bovine to human tuberculosis, and the source of the tuberculosis of animals other than cattle.

1. Turning first to the facts given in the preceding pages, we are confronted with a bacillus isolated from the tuberculous mesenteric glands of a child which was studied during an entire year in conjunction with a variety of other, both fresh and old, cultures from man, cattle, and other species, and which presents characters which we have ascribed to the bovine bacillus: (1) the short form; (2) the very feeble, sparse multiplication in cultures at the outset; (3) its virulence for

rabbits and guinea-pigs; (4) its power to produce extensive lesions in cattle, and (5) its reaction curve tending to and reaching a feebly alkaline level (phenolphthalein).

If bacillus XI. is not the bovine bacillus it would be impossible to place it at the present time, unless we put it among the cat bacilli. This, however, would not simplify our quest, since the three cat bacilli I have studied are to all appearances from cattle, and the third gave the reaction curve of the bovine bacillus, in spite of its reduced virulence.

It is not impossible, however, that tuberculous cats may infect children, and that the passage of bovine bacilli through cats might render them more acceptable to the human body. Leaving the tuberculosis of cats simply as a suggestion, I am inclined to adhere to direct infection from cattle, through milk, as the simplest explanation of the source of bacillus XI.

Since the appearance of my former paper in 1898, several investigators have found highly virulent tubercle bacilli in man. Vagedes[1] found one culture among twenty-eight isolated from man, which, it seems to me, was a bovine bacillus. I have already called attention to this culture,[2] and to the fact that, although the work was done under Koch, the latter failed to appreciate the significance of this discovery or else ignored it. Lartigau[3] also found at least one among nineteen human cultures of maximum virulence. Ravenel[4] has more recently described a culture designated BB, which has been more thoroughly tested than those mentioned. It was isolated through guinea-pigs from the mesenteric glands of a child seventeen months old. Death was due to tuberculous meningitis. There were ulcers in the ileum, and the mesenteric glands were caseous. The culture proved to be highly virulent for cattle. In submitting this culture, kindly sent to me by Dr. Ravenel, to the culture test, I found that its reaction curve agrees with that of human XI. and the bovine cultures tried, as shown in Table V., page 141. A second culture designated U was described by Ravenel as being perhaps of bovine origin. It was isolated from the mesenteric glands of a child three years old who had succumbed to tuberculous meningitis. There were miliary tubercles

[1] Zeitschrift für Hygiene, 1898, xxviii. p. 276.
[2] Medical News, February 22, 1902.
[3] Journal of Medical Research, 1901, vol. vi. p. 156.
[4] Loc. cit.

in the lungs, spleen, and liver. This culture, which was more virulent than the average human cultures, I was able to examine also. The reaction curve corresponded closely to that of the human type of bacilli, as shown in Table V. It will thus be seen that Ravenel's experience agrees with mine in that of two cultures isolated from mesenteric glands: one agrees with the human, the other with the bovine type.[1]

The medical literature of this subject has received since Koch's address in 1901 quite suddenly accessions from many sources; but few experimenters have taken the time necessary to isolate and carefully compare cultures. This literature does not, therefore, offer that precise basal information upon which far-reaching conclusions may be built.

De Schweinitz, Dorset, and Schroeder[2] briefly refer to one culture isolated from a child which has given them positive results in cattle. We must wait for the full report of this culture, which is promised in a bulletin of the Department of Agriculture. If I understand their deductions correctly the authors do not believe in the existence of any constant characters that distinguish races of mammalian tubercle bacilli. They believe that morphology and virulence are variable elements, and simply functions of culture media upon which they grow. This view I think would be rejected by all who have continuously studied bacilli from different species. Virulence necessarily declines with prolonged cultivation, and bacilli may assume slightly different forms on different culture media. These do not overthrow, but simply mask, racial characters.[3]

[1] Mention should be made here of a third case of tuberculosis of the mesenteric lymph nodes in a boy five years old. No other tuberculous lesions were found. The nodes sent to me by Dr. Mallory consisted in the main of the walls of a small cavity containing a soft, cheesy mass. In it tubercle bacilli could not be found. In none of three guinea-pigs which received suspensions of this cheesy matter into the abdomen could tuberculous lesions subsequently be found. The absence of living bacilli in this old, quiescent focus does not point to bovine tubercle bacilli as the cause. Cultures from abdominal lymph nodes of two cases of presumably primary food infection upon which I am now engaged exhibit thus far the characters of the human type of bacilli. They will be described in detail in a future paper.

[2] American Medicine, 1902, vol. iv. p. 850.

[3] The argument used by the authors in this paper, that the subcutaneous injection of a piece of lung tissue from a tuberculous child caused, within six months, as much evidence of tuberculosis in a calf as that which resulted from the subcutaneous injection of a virulent bovine culture after one year is not convincing, because the bovine culture used (III.) was isolated by me April 19, 1897, *i. e.*, it was four and one-half years old when used by Dr. de Schweinitz. The tubercle bacilli of whatever source become slowly attenuated in cultures, and comparative tests upon cattle are of little use when made, on the one hand, with fresh tissue; on the other with cultures several years old.

The interesting experiments of De Jong,[1] Fibiger and Jensen,[2] Schottelius,[3] and Orth,[4] do not contribute anything to the bacteriologic aspect of the subject, although they in general indicate that cattle may become diseased as a result of the inoculation of tuberculous tissue or cultures containing human bacilli. The experiments are performed under widely different conditions as regards the dosage and method of inoculation and the age of the animals employed. Thus Fibiger and Jensen used in several instances calves only ten to fourteen days old. De Jong used animals from one and one-half months to several years old.

In such experiments it might happen that the human bacilli used are actually of bovine origin. Thus, when Schottelius feeds mixed sputum from a number of cases of advanced phthisis and finds the animals tuberculous, it is possible that some one of the patients was suffering with the disease contracted from cattle. If so, the experiments simply show that the result would have been far more valuable if the bacilli had been isolated and the bovine type or race recognized at the outset. It is safe to predict that all work done with pathologic products of tuberculosis containing bacilli of unknown characters will have to be repeated with pure cultures.

2. The suggestive fact learned in the preceding pages that a culture of tubercle bacilli from the horse and the cat yielded the same reaction curve as the bovine cultures opens for more promising study the much-discussed subject of modification of virulence by passage through other species. The horse culture was from the start somewhat less virulent than bovine cultures. Cat III. was of decidedly reduced virulence. Yet both agree with the bovine type in tending toward or actually producing an alkaline reaction in glycerin bouillon. It seems probable that by studying these aberrant bovine cultures which apparently succeed only occasionally in infecting other species we may reach some better understanding concerning the extent to which bovine bacilli may be modified in other hosts. That these species should possess and transmit a tubercle bacillus of their own seems improbable, though not impossible, and it should be kept in mind. The solitary culture from the dog which I have isolated was to all appearances human in type. But the culture was lost before the culture reaction test could be applied.

[1] De Einheid der Zoogdiertuberculose, Leiden, 1902.
[2] Berliner klin. Wochenschr., 1902, No. 38.
[3] Münch. med. Wochenschr., 1902, p. 1610.
[4] Berliner klin. Wochenschr., 1902, No. 34.

Until further studies are made, domestic pets, especiallly cats and dogs, should not be lost sight of in the endeavor to trace tuberculous infection to its source.

Further bacteriologic studies are also needed to determine as far as possible the relative number of cases of tuberculosis in man due to cattle, so that the practical preventive measures to be employed may bear some economic relation to the injury inflicted. That these in the past have been out of proportion to the danger incurred seems more than probable.

There remains still one feature of the subject before us upon which I have not touched. This is the varying virulence of tubercle bacilli isolated from man, excluding those which I have referred directly to cattle. That a considerable range of pathogenic power is possessed by such bacilli had been made evident by Vagedes, Lartigau and very recently by Veszpremi.[1] Similar variations have been noticed by the writer, but they sink into insignificance when contrasted with the virulence of bovine bacilli, and I have not attempted to grade them by special inoculations. It is of great importance to determine whether any sharp line of demarcation can be drawn through these varieties by the culture test I have described, and whether we may thereby be put into the position of tracing modified bovine bacilli in the human body. The difference between the bovine and the human type appears to consist in part in a different behavior toward glycerin in cultures. Unless this difference is merely quantitative and not qualitative, it is likely to persist in the different hosts. If this should prove true eventually, we may be able to detect degrees of virulence in bovine cultures, and they would then represent degrees of adaptation to another host tending toward a final type in that host. Variation in virulence is a phenomenon which is probably founded upon important principles of parasitism, and its relation to origin or source of the bacteria in another host needs careful investigation.

Conclusions.

1. The conception of a bovine and a human type of tubercle bacilli introduced by me in 1898 is confirmed and still further defined. This conception does not exclude that of intermediate types likely to be found in other species.

[1] Centralbl. f. Bakt., 1 Abth., Originale, 1903, xxxiii. p. 176.

2. Tubercle bacilli not distinguishable from the bovine type or race are occasionally encountered in the human subject.

3. From their action upon glycerin bouillon mammalian tubercle bacilli may be divided into two groups : one corresponding to the human, the other to the bovine type.

4. Mammals other than cattle are probably infected either from cattle or man or from both sources.

5. The problem of the modification of biologic and pathogenic characters of tubercle bacilli in foreign hosts is best approached by a comparative study of tubercle bacilli from different mammals.

DISCUSSION.

DR. OSLER : Were there any macroscopic differences between the mesenteric glands in the two cases? Many years ago Dr. Creighton suggested the fact that some cases of human tuberculosis might be of bovine origin on account of the similarity of the lesions.

DR. SMITH : In answer to Dr. Osler's question, I would state that I did not see the autopsies, but the protocols are given in full in the paper. In the case in which the culture turned out to be bovine, the mesenteric glands contained large numbers of the bacilli, whereas in the gland from which bacilli of man were isolated they were very scarce. The general pathologic conditions as revealed by the autopsy are much alike in the two cases.

DR. OSLER : It would be interesting for those working on this subject to determine whether the lymphatic type of tuberculosis in man, which seems so definite, is more closely allied to the bovine type.

EXPERIMENTAL STUDIES ON THE EOSINOPHILIA OF TRICHINOSIS.

A Preliminary Report.

By HERBERT U. WILLIAMS, M.D., and CHARLES A. BENTZ, M.D.,
of Buffalo, N. Y.

(From the Pathologic Laboratory of the University of Buffalo.)

The work of Brown[1] and numerous others has shown that during an acute attack of trichinosis in man a marked increase of eosinophilic leukocytes occurs in the blood in most cases. Furthermore, numerous eosinophiles are found in the muscular tissue near the worms. In cases of infection with other parasitic worms an increase of eosinophiles in the blood has also been recorded. Various observations have suggested that parasitic worms produce poisons analogous to bacterial toxins.

Several Italian investigators[2] claim that they have obtained substances from species of tenia that were very toxic to animals. These substances were also chemotactic for eosinophiles.

Eosinophilic leukocytosis becomes of additional interest from its bearings on the subject of leukocytosis in general and its relations with infections of different sorts. Numerous investigations[3] have shown that eosinophilic cells may be quite numerous in various normal and pathologic processes. No conclusions can be drawn from any condition of increase unless it is marked enough to constitute a distinct reaction.

The present writers began the study of eosinophilia in trichinosis by feeding fresh pork containing trichinæ (trichinella, Stiles) to rats and cats. Trichinosis was readily produced, and the muscles

[1] Journal of Experimental Medicine, 1898, vol. iii.
[2] Messineo and Calamida. Centralblatt für Bakteriologie, 1901, Bd. xxx.
[3] See Howard and Perkins. Johns Hopkins Hospital Reports, 1902, vol. x.

containing the parasites and the blood were studied. No increase of eosinophilic cells in either situation was noted, or else the results were so slightly marked as to be indecisive. Numerous eosinophiles were, however, sometimes found about the encapsulated worms in the muscles of hogs in whom the infection had occurred naturally.

The writers then endeavored to secure trichinæ in a concentrated form and in considerable quantity by the artificial digestion of trichinous pork. The substance obtained was then inserted into animals, and the results with respect to any general or local increase of eosinophilic cells were noted.

Experiments with Dried Trichinæ. Fresh pork, containing numerous trichinæ, was cut into small bits and freed from fat as far as possible.[1] It was then digested at 36° C. for forty-eight hours in artificial gastric juice, containing pepsin and 0.2 per cent. hydrochloric acid. Bacterial contamination was avoided as far as possible, and only a slightly sour odor was given off. The sediment was collected on a sterile filter, freed from visible masses of tissue and fat, and washed with sterile distilled water. In favorable cases one-fourth to one-half of the bulk of the sediment consisted of worms. The remainder was made of fat, with shreds of muscle and fibrous tissue. Many of the worms were still moving actively. We have found them perfectly vigorous after four days' digestion in the incubator. After washing, the sediment was dried over the water-bath at 50° C., as rapidly as possible, with the aid of the vacuum-pump. In our experiments we have seen no evidence of vitality in the worms after this drying. Although bacteria could not be entirely excluded, no odor of putrefaction was perceptible. The dried residue was stored in sterile tubes, kept in tightly stoppered jars, with sticks of caustic soda.

The residue, containing the dried trichinæ, was placed in sterile collodion cups, which were inserted into the abdominal cavities of a number of cats and dogs. The results were noted after periods varying from four to twenty-two days. The collodion and the mass of tissue around it were removed entire, fixed in Zenker's fluid, embedded in paraffin, and stained in the Biondi-Heidenhain

[1] For numerous specimens of pork we are indebted to Dr. Salmon and to Dr. Dyson, of the Bureau of Animal Industry.

mixture. In favorable cases a well-marked accumulation of eosinophilic leukocytes occurred around the collodion. Often the pictures obtained were very striking, and much like the collections of eosinophiles seen about trichinæ in hog's muscles. The eosinophiles were usually separated from the collodion by a zone of non-granular leukocytes. We obtained one positive result using a closed collodion sac, which was apparently intact when removed. In all we secured positive results in three out of eight cats, and three out of five dogs. The negative results were probably in part due to suppuration, which occurred a number of times. Examinations of the blood were made in all cases, but no increase of the eosinophiles was observed.

Control Experiments. It was, of course, appreciated that the collections of eosinophilic cells might have been due to some product of digestion contained in the residue or to some product of bacterial action on the tissues which had no relation with the dried worms. Normal hog's muscle was digested in the same manner, and was similarly inserted into the peritoneums of cats and dogs. In three dogs the results were negative. In three out of five cats the results were entirely negative. In two cats moderate numbers of granular cells appeared. The granules were, however, much smaller and less distinct than those in genuine eosinophilic leukocytes, besides being of a much paler color. They probably belong to the class of leukocytes often called pseudoeosinophiles.[1]

Experiments with Frogs. As the frog is not susceptible to infection with living trichinæ, any results obtained would probably be due to substances contained in the bodies of the worms introduced.

It is well known that parasitic worms are very common in the alimentary canal of the frog. The stomachs and intestines of all the frogs used were examined at the autopsies for parasites in general. As was to be expected, nematode worms were frequently found. We are unable to see that their occurrence had any relation to the results hereafter described as positive or negative.

Through small cuts in the skin and muscle in the middle line a fine, sterile glass canula was pushed into the peritoneum. A drop of fluid was withdrawn, smeared on a cover-glass, stained,

[1] See Hirschfeld. Virchow's Arch. f. path. Anat., etc., 1897, Bd. cxlix. p. 39.

and examined. Eosinophiles were only occasionally found. Through the same canula, a small mass of the dried worms was pushed with a sterile platinum wire. No marked increase of eosinophiles in the peritoneum occurred before the fourth day. In each of five frogs examined after the eighth day the increase was very striking. It was found as late as the thirty-second day. The injected material was surrounded by a yellowish mass adherent to the liver, stomach, and intestine. The greater number of eosinophiles occurred around the edges of this mass. Often free eosinophilic granules were numerous. The cells were studied, for the most part, in smears made on cover-glasses. The stains employed were Wright's method, and eosin and methylene blue after fixation in alcohol and ether. An increase of eosinophiles in the blood was seen once only.

Control Experiments. Eighteen frogs were used for control experiments. The substances introduced into the peritoneum were the dried residue from the digestion of normal pork, Witte's peptone, pure pepsin, and Liebig's beef extract. They were inserted in the manner above described. Cover-glass preparations made as in the preceding cases and after similar intervals gave uniformly negative results. Occasionally, eosinophiles were fairly common in the peritoneal fluid, but they were not to be compared in numbers with those found where the dried trichinæ were used.

The *stability* of the substance which produced the collections of eosinophiles was also tested. A specimen of residue containing dried trichinæ which had been kept for nearly two years was used. Another specimen, more recently made, was digested for a week in alcohol and a week in ether. Some of the latter was subjected to a temperature of 80° C. dry; some to 100° C. dry. Another portion was made into a suspension with normal salt solution and boiled for five minutes, while still another portion was boiled for five minutes on two consecutive days. Seventeen frogs were used for these tests. In general it may be said that the proportion of positive results was much reduced, but that none of these procedures destroyed the activity of the substance entirely. Extraction with alcohol and ether produced the least and prolonged heating the greatest effect.

Remarks. In all the experiments related above, it must be admitted that bacteria were not excluded; in fact, their presence was usually obvious at the autopsies. Our next effort will be to secure a sterile product, possibly by filtration through porcelain. Our control experiments seem to us to compensate for such possible sources of error to a considerable extent. Also, the samples of dried trichinæ which we used in the various experiments were made on several different occasions, and the same source of error would not have been likely to enter more than once. That becomes even less probable considering that animals so different as the dog and cat and the frog all gave similar results.

Conclusions. The residue left from the digestion of trichinous pork with artificial gastric juice contains numerous trichinæ. The dried residue introduced into dogs, cats, and frogs causes eosinophilic leukocytes to collect about it in large numbers, although not in every case. This action is due to some unknown substance, probably derived from the bodies of the worms. However, the experiments do not entirely exclude the possibility that the results obtained might have been due to some product due to the action of hydrochloric acid and pepsin on pork, or to the agency of bacteria. The interpretation of our results may also be modified if it should be shown that similar collections of eosinophiles appear after the introduction of many other and unrelated materials.[1] The substance studied by us has not shown itself to be powerfully toxic. It is somewhat diffusible; the eosinophiles are most numerous at points a short distance from the mass introduced. The substance is not wholly removed by maceration in cold alcohol and ether. It has some resistance to heat. Its properties remain unimpaired for several months.

[1] Hardy and King found that numerous leukocytes, and among them many eosinophiles, appeared after the introduction of urare into the lymph spaces of the frog.—Journal of Physiology, 1894, vol. xv.

THE CLINICAL ASSOCIATIONS AND SIGNIFICANCE OF THE CARDIOPULMONARY MURMUR.

By JAMES J. PUTNAM, M.D.,
OF BOSTON.

The cardiopulmonary murmur has been regarded by most physicians as of somewhat accidental occurrence, indicating, perhaps, some unusual relationship of the heart and lungs, and almost certainly due to compression or aspiration of a piece of lung by the contracting heart, but as of no clinical significance except in so far as it was liable to be mistaken for a sign of valvular lesion. Such was my own supposition until—a good many years ago—I became impressed with the relative frequency of its occurrence among certain classes of patients, namely, young and middle-aged male neuropathics and asthenics, who were often spare in build, long chested, and usually with rather weak muscular systems and (I should now add) elastic chest walls. Subsequent investigations have fully confirmed this impression, while, meantime, the finding of corroborative statements published by various other observers has increased my confidence in its substantial correctness. When anything is said at all, by those who have written upon the subject, about the general nutrition and characteristics of the persons among whom this murmur has been found, some such description as that just indicated is usually given, or, as is often the case, it is noted that the patient has presented signs of pulmonary tuberculosis.

For the past two or three years I have paid closer attention to this clinical relationship between the cardiopulmonary murmur and the neuropathic and asthenic tendencies, and offer my experience thereon in a preliminary form, together with certain other facts which may help to broaden our conception of the possible significance of the sign.

Potain, who, after Laennec, was the pioneer in the clinical study of these sounds, groups together as cardiopulmonary or exocardial all the so-called "functional" heart murmurs, including those usually classed as hemic. Recent studies (as those of Prince, Stengel, and Arnold in this country) have, however, made it clear that this is an incorrect classification, and that the major parts of the "functional" murmurs are due to defective co-ordination, defective action, impaired nutrition, and relaxation of the cardiac muscles and of the arterial walls.

The cardiopulmonary murmurs are of different origin, and yet they, too, are heard pre-eminently under some of the conditions which favor the occurrence of the "muscular relaxation" sounds, namely, during disturbed innervation. Not infrequently they disappear during the course of a somewhat prolonged examination.

They are not especially characteristic of acute anemia and the excessive fatigue following athletic exercises (Stengel and Arnold), but they are temporarily accentuated by the nervous excitement attending an examination of the heart, as in the case of men offering themselves as candidates for positions on the police force (Prince and McCallum). Both sorts of murmurs occur under these conditions, and may disappear before the examination is over. It is, indeed, not certain that it is always possible to distinguish between them, though the fact that the cardiopulmonary sound ceases at the end of a forced expiration is probably decisive under ordinary circumstances.

There is, however, another relationship of the cardiopulmonary murmur which is of special interest, namely, that to the interrupted, or cogwheel respiration, or "heart breath," that form of respiration, namely, where the inspiratory sound, instead of being continuous, is rhythmically broken by accentuated puffs corresponding with the contractions of the heart.

Although it is true that tuberculous consolidation favors the conduction and perhaps the occurrence of these respiratory sounds, yet careful physiologic studies have shown that the phenomenon is, in its main features, to be detected under normal conditions, and these studies acquire a special interest when it is admitted that there can be no radical difference between the interrupted respiration and the cardiopulmonary murmur. Both sounds are due to

displacement of air through the heart's action or the blood current, and both are heard, not infrequently, in the same subject. When this is the case, it is my experience that to the ear (or stethoscope) placed near the apex or over the body of the heart, it is the cardiac element which makes the strongest impression, while at the base, or, as sometimes, in the axillary line, the sound which is heard is of such a kind that one is no longer tempted to classify it as a cardiac murmur at all, but as an interrupted inspiration. Yet the differences must be of degree, essentially or alone.

The physiologic studies which have been alluded to as establishing the fact that the respiration of normal animals is modified, directly or indirectly, by the heart's action, have been discussed by Dr. S. J. Meltzer, and the conclusion reached by him, partly on the basis of original experiments, is in favor of the view that this effect is due, not to the changes in size and position of the heart itself, but to displacement of air attending the propulsion of blood through and out of the chest. Under ordinary conditions the amount of influence exerted on the respiration in this way is but very slight, but I presume there can be no doubt that the "cog-wheel" respiration (or one form of it if there be more than one) is only an exaggeration of this (normal) phenomenon which is discoverable by careful tests.

Although the rules given by Potain and others doubtless serve, as a rule, to distinguish the cardiopulmonary murmur, yet, inasmuch as there is not one of them that is not sometimes violated, there seems to be some question whether it is always possible to differentiate the cardiopulmonary murmur with positiveness from that which has been called neuromuscular, and I am free to admit that in my own past observations I may have failed, in a few cases, to differentiate between them with sufficient care. It is, indeed, not very uncommon to find a transient murmur of very slight intensity, heard at or near the apex, especially, I think, in men, which disappears before one has the opportunity to fully satisfy himself as to its nature. After allowing for errors of these sorts, however, I feel justified in the statement that the true cardiopulmonary murmur is very rarely to be detected among vigorous and not nervous persons of either sex, even where such persons are temporarily ill with what might be called sthenic diseases. On the other hand,

it occurs with relative frequency among markedly neuropathic and asthenic males, but, again, not nearly so often among females, even when neurotic and poorly nourished. This is especially striking, in view of the fact that the murmur of the left base, which is so very common among feeble and anemic women, is very rare among feeble men.

In order to ascertain approximately the actual and relative frequency of the cardiopulmonary murmur, I have looked over the records of 400 private patients whom I have examined during the year and a half since the beginning of 1902, one-half of the 400 cases having been classified in general terms as neurasthenic or neuropathic, and the other half as representing disorders of other sorts.

The cardiopulmonary murmur was heard in about 30 of these 400 cases, there being, of course, a few that were doubtful. Of these 30 cases at least 26 belonged in the neurasthenic group, and only 4 in the non-neurasthenic. Even as regards these there was some question as to the group in which they should be placed. As regards sex, 26 of the 30 patients were men and four women. These figures recall a tabulation by Matthews (*Provincial Medical Journal*, 1901, vol. ii. pp. 116–121), of Providence, R. I., who reports on 32 patients, of whom 23 were men and 9 women, though saying at the same time, "I am not aware that sex has any influence in the production of this sound." On the other hand, Squire, of London, reported 23 cases in 1898, of which 13 were the cases of men, and 10 of women ; 14 of these patients, however—9 men and 5 women—had pulmonary tuberculosis.

As a check to my own observations I have recently asked several gentlemen who have occasion to examine large numbers of patients in the Out-Patient Department of the Massachusetts General Hospital to listen for this murmur with especial care, and their investigations confirm my own. In the men's room the cardiopulmonary murmur is of rare occurrence, at least in a pronounced form ; not more than three or four examples having been found in the examination of four hundred or more persons. In the women's room it is somewhat more common, perhaps occurring in 2 per cent. of the cases. In the neurologic department, however, in the special class of patients to which I have referred, namely, the pronounced

neuropathic and asthenics, it has been found in 8 or 10 per cent. As regards the diagnostic characters of the cardiopulmonary murmur, I can corroborate the statements of those who have noted its occasional presence as well during the diastole as during the systole of the heart, and the fact that it may be heard in the axillary line and even at the back. On the other hand, I cannot find that the murmur depends to any obvious extent upon the rapidity or turbulence of the heart's action, or that it is at all necessarily influenced by changes in the position of the patient. Further studies may correct this view.

The fact that the murmur is made to disappear by forced expiration has been repeatedly made use of as affording a hint as to its origin. The difficulty in the way of explaining this expiratory disappearance seems to me, however, to be considerable, and to be still greater when regarded in the light of another fact which I have observed, namely, that a similar disappearance can sometimes be brought about by the strong compression of the chest wall by an assistant while auscultation is going on. Furthermore, it is noteworthy that after being banished through this procedure the murmur does not always return at once or perhaps even during the remainder of the examination.

The fact, now abundantly substantiated, that the cardiopulmonary murmur, if not heard exclusively among neuropathics, constitutional asthenics, and tuberculous patients, is heard far oftener in them than in any others, still demands an explanation. If this is found it may throw much light upon the origin of the sign. In fact, the patients belonging to these groups present several interesting peculiarities which may be more or less important in this connection.

In the first place, the heart muscle in these cases is liable to be weak, the innervation defective, and the beat tumultuous, irregular, rapid, or of changing rhythm. In the next place, the chest wall may be unduly yielding, more or less collapsed from early rickets or other nutritive disorders, or otherwise deformed. The thorax has indeed been repeatedly noted as unusually long and slenderly provided with muscles. Finally, the lung may contain tuberculous deposits or cavities, or may be abnormally placed with relation to the heart. On the other hand, there is no single

one of these peculiarities which is universally present. The neuropathic patients do not always have deformed or feeble chests ; the poorly nourished persons are not always markedly neurasthenic or neuropathic. Again, it must be admitted that the cardiopulmonary murmur itself is not heard with such frequency, even among that class of patients who have it relatively often, as to imply a necessary concomitance with any particular signs or symptoms of other sorts.

There is, however, one possible way of regarding the sign under discussion, which clothes it with special interest and at the same time makes the task of explaining its genesis slightly easier. The cardiopulmonary murmur may, namely, be classed with the numerous peculiarities or stigmata which are met with so often among neuropathic persons and yet are not always present and do not always imply, of necessity, a neuropathic constitution.

If the ranging of this murmur under such a head as this does not yield a true account of its pathogenesis, it does provide a new point of departure from which an explanation may be sought.

The researches of later years have shown, with increasing clearness, that it is not alone in connection with such toxic affections as myxedema that changes of bodily type, of definite form, occur. There are many other tendencies as well, which are as far reaching if not so serious in their action. The stigmata of constitutional neurasthenia are multiple and within certain limits fairly constant ; and they include such different states as nutritive disorders of the skin and its appendages, abnormalities in the formation of the thorax, prolapse of the abdominal viscera, and, on the other hand, a great variety of peculiarities of the life and functions of the nervous system. It is only to a few of the abnormalities that I wish to call attention in this connection, and these are the changes in the thorax, the enteroptosis of Glenard, and the vasomotor disorders ; or in general, the disorders of innervation of the heart and bloodvessels.

It is in just the class of patients whom I have described as particularly liable to the cardiopulmonary murmur, namely, among the slender, rather feeble neurasthenics, that the tendency to ptosis of the abdominal viscera is pre-eminently found, but more commonly in women than in men. Stiller, who has had a large experience in abdominal examinations, discussed this point some years ago, and

pointed out at the same time another stigma of neurasthenia to which this same group of persons is also liable, namely, a relatively loose attachment of the tenth cartilage of the right side to the thoracic cage. I have found the cardiopulmonary murmur to be present in connection with both of these signs, though the association is by no means invariable or necessary. It will be remembered in this connection that it is the right kidney which is especially liable to prolapse. The innervation of the heart and arterial system is peculiarly apt to be affected in neurasthenics. Thus, Erben (*Wiener klin. Woch.*, 1898, No. 24) finds that slowing of the pulse to the extent of three to six beats is apt to be brought on by bending over once or twice, or by throwing the head backward, and this change is but slowly recovered from. Again, irregularity and rapid beating of the heart are easily brought on by efforts of various sorts. In view of such facts as these, it has seemed to me not impossible that among the causes for the cardiopulmonary murmur it might be reasonable to think of some abnormality or defect of the innervation by which the action of the heart is brought into relation with that of the lung. It can hardly be doubted that some such mechanism as this exists, for we know that at every expiration and every inspiration the conditions of the cardiac circulation are altered, and it would be a strange anomaly, indeed, if this change failed to be registered and regulated through the action of the nervous system. Surely, a purely mechanical explanation of the cardiopulmonary murmur is inadequate. For why should an overlying piece of lung be aspirated or compressed by the passage of the blood through the chest of a nervous and feeble person, and not by that of a vigorous and healthy man? The task of explanation becomes much easier if we may assume that the regulatory mechanism governing the tension of the lung or the tension of the vessels has been damaged, or that the relation between the two has become defective. One may imagine, for example, some such disturbance to exist as is seen when a swinging pendulum receives a knock which imparts to it a twisting movement that only gradually passes away. Similarly, perhaps, under the influence of excitement, the co-ordination of the respiration and the heart's action or the vascular tension may become disturbed, and yet be restored by the compression of the chest or the action of forced expiration. I

do not pretend that even this explanation is an adequate one, but only that it may serve as the prototype of some other which is really satisfactory.

List of References.

Arnold, H. D. Systolic Mitral Murmurs; their Transmission, with Special Reference to the Nature of So-called Anemic Murmurs. Journal American Medical Association, Chicago, 1899, xxxiii. 139–144.

Barié, E. Les souffles cardio-pulmonaires diastoliques. Bull. et mém. Soc. d. Hôp. de Paris, 1896, 3 s. xiii. p. 295

Bonnet, L. Bruits pulmonaires rhythmés par le cœur; caractères et siège insolites. Lyon méd., 1897, lxxxvi. 39–44.

Braun u. Fuchs. Neuras. Pulsphaenomen. Centralb. f. inn. Med., 1902, No. 49.

Carslaw, J. An Unusual Case of Cardiopulmonary Râle. British Medical Journal, London, 1899, ii. 1883.

Drummond. Lancet, April, 10, 1897.

Foshay, P. M. A Case of Cardiopulmonary Murmur Illustrating the Importance of Differentiation. Medical Examiner and Practitioner, New York, 1901, xi. 337–339; Cleveland Journal of Medicine, 1901, vi. 236–239.

Gibson, G. A. Cardiac Murmurs, Diseases of the Heart and Aorta, 1898, 155–174.

Hoover. New York Medical Journal, August 6, 1898.

Huchard, H. Les faux cardiaques (souffles cardio-pulmonaires). Bull. méd. Paris, 1896, x. 257–260.

Huchard, H. Exemples de souffles cardio-pulmonaires à foyers multiples, très intenses, simulant un rétréssement mitral avec insuffissance, et surtont une insuffissance aortique. Bull. et mém. soc. méd. d. hôp. de Paris, 1896, xiii. 298–294.

Matthews, G. S. Endocardial and Exocardial Murmurs. Provincial Medical Journal, 1889, ii. 116–121.

McCollom, J. H. Boston Medical and Surgical Journal, 1889, vol. cxx. p. 103.

Meltzer, S. J. On the Nature of Cardiopneumatic Movements. American Journal of Physiology, vol. i.

Potain. Les caractères des souffles extracardiaques. Méd. Mod., Paris, 1893, iv. 110-113.

Potain. Clinique méd. de la Charité, 1894, 371.

Prince, Morton. New York Medical Record, 1889, vol. xxxv. 421.

Sahli. Lehrbuch der Untersuchungsmethode.

Sanders, G. Cardiopulmonary Murmurs. Edinburgh Medical Journal, 1896, 97, xliii. 522, 529.

Schroeder. Functional or Inorganic Heart Murmurs. New York Medical Journal, 1898, 228.

Squire, J. E. A Cardiopulmonary Murmur; or a Respiratory Murmur Rhythmical with the Heart Beats. British Medical Journal, London, 1898, ii. 1740-1742.

Stengel, A. The Significance of Systolic Murmurs Over the Apex and Base of the Heart. Cleveland Journal of Med., 1898, ii. 191–203, p. 195.

Stiller. Enteroptose im Lichte eines neuen Stigma Neurasthenicum. Arch. f. Verdauungskr., Bd. ii. Heft. 3, p. 285–289. See also Berliner klin. Woch., 1902.

Talma, S. Experimentel erzeugte, "anorganische" Herzgeräusche. Berl. klin. Woch. 1898, xxv. 1037–1039.

TYPHOID FEVER: AN ANALYSIS OF 717 CASES.

By JOHN McCRAE, B.A., M.B. (Tor.)

(From the Pathologic Laboratory of the Montreal General Hospital.)

This series comprises all cases in which the diagnosis is reasonably sure, admitted to the wards of the Montreal General Hospital from January 1, 1897, to December 31, 1902. Several cases admitted after perforation had occurred are included, as these reasonably must be included in a hospital death rate.

Time of Incidence. The minimum admissions occur in February, the number gradually increasing to the end of August, the latter month showing the maximum number. Despite the severity of the winter, the number existing up to the beginning of February is noteworthy.

Month.	*Admissions.*	*Month.*	*Admissions.*
January	4.9 per ct.	July	10.8 per ct.
February	2.5 "	August	15.8 "
March	2.6 "	September	12.2 "
April	5.0 "	October	12.7 "
May	7.3 "	November	9.4 "
June	9.3 "	December	7.3 "

Mortality. The mortality was 66, or 9.2 per cent.

Sex. Male 65.3 per cent.; female 34.7 per cent. Of the deaths, 71.2 per cent. were males; 28.8 per cent. were females.

Age.

Age in years.	*Number of cases.*	*Per cent. of cases.*	*Number of deaths.*	*Per cent. of deaths. (approx.)*	*One case died (approx.) in every*
1 to 5	7	0.98	1	1.5	7
6 " 10	31	4.3	1	1.5	31
11 " 15	67	9.3	2	3.0	33
16 " 20	160	22.4	12	18.0	13
21 " 25	174	24.4	14	21.0	12
26 " 30	117	16.3	10	15.0	11
31 " 35	70	9.8	7	10.5	10
36 " 40	47	6.5	6	9.0	8
41 " 45	20	2.8	5	7.5	4
46 " 50	15	2.1	5	7.5	3
51	6	0.8	3	4.5	2

Etiology. Previous attack of typhoid is described in 21 cases (2.96 per cent.); 1 case one year before, 3 two, 3 three, 2 four, 2 seven, 2 eight, 1 nine, 2 ten, 1 eleven, 1 fourteen, and 1 twenty-one years; in 2 the time is not stated. Four cases developed in the hospital; one patient developed the disease after thirty days in the hospital; two nurses and one hospital orderly contracted it while in attendance on typhoid patients.

Duration. Excluding fatal cases and a small number in which the beginning of the disease could not be accurately determined, the average duration of the febrile period for 640 cases was 27.2 days. The length of illness and convalescence, measured from the day of onset to the day on which the patient was discharged, averaged for 619 cases 52.2 days.

Degree of Fever. For purposes of classification arbitrary divisions were made between high and moderate fever: fever which was below 104° was classed "moderate;" 104° or over during four days (or less) was classed "moderate with occasional high range;" and "high" was used to describe fever which reached 104° on more than four days. Of 713 cases, 419 (59 per cent.) were moderate; 110 (15 per cent.) were moderate with occasional high range; 184 (26 per cent.) were high.

As a rule, fatal cases showed high temperature, although in 66 fatal cases the temperature was moderate in 21 (32 per cent.).

The Cardinal Points of Diagnosis. The so-called Widal test was tried in 678 cases; it was positive in 629—*i. e.*, 92.77 per cent. of cases tried.

Ehrlich's test (Diazo reaction) was tried in 512 cases; it was positive in 344—*i. e.*, 67.2 per cent. of cases tried.

Rose spots were observed in 467 cases, equivalent to 65 per cent. of all cases.

The spleen was palpated in 341 cases, equivalent to 47.5 per cent. of all cases.

Symptoms of Onset. No note was made of complaint of anorexia; the following common signs of onset were noted:

Weakness, definite complaint	55.0 per cent.	(of 317 cases.)
Headache	66.4 "	(" 717 ")
Pain in back, limbs, etc.	37.4 "	(" 717 ")
Pain in abdomen	22.7 "	(" 717 ")
Tenderness in abdomen upon pressure	12.5 "	(" 400 ")
Constipation	21.2 "	(" 717 ")
Diarrhea[1]	25.4 "	(" 717 ")
Vomiting	20.6 "	(" 717 ")
Epistaxis	15.0 "	(" 717 ")
Chill (definite rigor)	8.6 "	(" 717 ")
Sore throat	3.5 "	(" 717 ")

Symptoms of the Course. The condition of the bowels was as follows: Constipation marked the course of the disease in 345 cases (48 per cent.), diarrhea in 118 (16.5 per cent.); the bowels were normal during the disease in 95 cases (13 per cent.). The symptoms so much complained of at onset rarely persisted, headache during the course being noted in but 38 cases, bodyache in 13; delirium was noted in 102 (14.2 per cent.); epistaxis was present during the course in 24 cases (3.3 per cent.), vomiting in 72 (10 per cent.), chill in 36 cases (5 per cent.); the last was frequently explicable by some complication which had supervened. Pain in the abdomen is an extremely frequent symptom of the course of typhoid fever; in this series it has been noted in only 22.7 per cent. of the cases, although it actually occurs in a much greater percentage of all cases. Tenderness upon pressure is noted in 50 (12.5 per cent.) of 400 cases. Abdominal pain occurs at any period of the disease, and complaint of it will depend largely upon the character of the patient. Dicrotism of the pulse was mentioned in 106 cases (14.8 per cent.).

Relapse, etc. A true relapse was present in 64 cases (8.9 per cent); 6 cases had two and 1 had three relapses. In 51 cases the febrile period averaged twenty-five days, the interval of normal temperature 6.3 days, and the relapse 15.5 days; four second relapses averaged twelve days normal temperature, followed by sixteen days relapse; a third relapse was preceded by fourteen days normal temperature, and lasted ten days. Intercurrent relapse

[1] In 2.2 per cent only of these is the diarrhea stated to be the result of purgative medicine; this figure is probably far too small.

occurred in 48 cases (6.7 per cent.), in 46 of which the main febrile period averaged 25.9 days, the relapse 18.8 days; many cases of long-continued fever without remission are similar to intercurrent relapse, but none has been included save those which show a distinct relapse rising gradually from a well-defined minimum point of the fever.

Recrudescence occurred in 61 cases (8.5 per cent.), "steeples" (*i.e.*, church-steeple-like rises on one or two successive days of normal temperature) in 49 (6.9 per cent.), thrice immediately after semisolid food. It will be seen that, roughly, 31 per cent. of all cases suffered from a rise of temperature to a noticeable degree after the regular course was finished.

Frequent complications occurred as follows:

Bronchitis (including pharyngitis)	192 cases	(26.8 per cent.)
Neuritis	26 "	(3.5 ")
Abscess	47 "	(6.5 ")
Phlebitis	25 "	(3.4 ")
Otitis media	16 "	(2.2 ")

Neuritis (including tender toes) followed bath treatment in 19, sponging in 1, and antipyretics in 4 cases. Abscesses were most frequent in the axillæ, affecting the rest of the body, limbs, and head in the order named. Staphylococcus was found in 7 cases, Eberth's bacillus never. In 18 cases phlebitis affected the left side in 12, the right in 3, both in 3; it never occurred before the middle of the third week, and often not until the sixth.

Infrequent Complications. The following are stated in numbers of cases (717 cases):

Integument, etc.:		
Carbuncle	1	
Cellulitis	2	
Conjunctivitis	2	
Erysipelas	1	
Erythema	7	
Furuncle	6	
Herpes	3	
Tache cerebrale	6	
Ulcers	1	
Urticaria	1	
Alimentary system:		
Cholecystitis	3	
Glossitis	3	(1 syphilitic)
Icterus	2	
Parotitis	1	
Stomatitis	4	

Respiratory system:	
Empyema	2
Pharyngitis, etc.	8
Pleuritis	13
Pneumonia	8
Osseous, muscular systems, etc:	
Arthritis	1
Mastoiditis	1
Myositis	2
Osteomyelitis	5
Periostitis	4
Generative system:	
Abortion	2
Mastitis.	2
Urinary system:	
Cystitis	9
Pyelitis	3
Nervous system:	
Paralyses[1]	2
Post-typh. insanity	5
Tetany	2
Circulatory system:	
Dilatation of heart	14
Pericarditis	1

The number of cases noted to have had cardiac dilatation is doubtless far from the true number, but slight differences of size of the heart and transitory murmurs, indicating temporary dilatations are uncertain signs, and in the hands of house physicians of comparatively short experience are apt to be overlooked. So also many passing myocarditides of slight degree must escape notice.

Associated conditions:	
Alcoholism	1
Arteriosclerosis	1
Cardiac valve lesions	16
Chlorosis	3
Diphtheria	1
Epilepsy	2
Gonorrhea	4
Hysteria	4
Neuritis, alcoholic	1
Orchitis	1
Parasites	..
Ascaris	5
Tenia	1
Pregnancy[2]	5
Rheumatism, acute	2
Syphilis.	3
Tuberculosis, pul.	6

[1] One case had muscles of the face partially paralyzed, the other the muscles of deglutition.

[2] In two cases abortion at first and second month occurred; pregnancies of five, six and a half, and seven months were uninterrupted.

Hemorrhage. Hemorrhage occurred in 72 cases (10 per cent.), of which 26 proved fatal; in 11 cases hemorrhage and perforation were associated. In 31 of these 72 cases there are notes of the time at which food other than purely liquid was given; of these 31, 12 cases had such food before hemorrhage occurred. Although the notes are not absolutely explicit, it may be presumed that such diet was continued up to the time at which hemorrhage occurred, and the space of time between the administration of such food and the occurrence of hemorrhage varied from a few hours up to twenty-nine days; the exact figures are as follows: immediately, 3, 5, 6, 7, 9, 10, 11, 12, 12, 13, 26, and 29 days.

Hemorrhage occurred oftenest at the end of the second week and at the middle of the third. By weeks it occurred as follows:

First week	1 case.	Fifth week	4 cases.
Second week	22 cases.	Sixth "	7 "
Third "	20 "	Seventh week	1 case.
Fourth "	15 "		

By days it occurred as follows:

4 to 7 days	1	25 to 28 days	10
8 " 12 "	10	29 " 31 "	2
11 " 14 "	12	32 " 35 "	2
15 " 17 "	8	36 " 38 "	2
18 " 21 "	12	39 " 42 "	5
22 " 24 "	5	43 " 45 "	1

The earliest initial hemorrhage was upon the fifth day, the latest on the forty-fourth day. This complication occurred oftenest, proportionately, in cases treated by baths, and least often, proportionately, in those treated by antipyretics.

Perforation. As stated above, perforation occurred 43 times; 23 cases were operated upon, of which 6 recovered. These six were operated upon at various times (from one and a half to fifteen hours) after perforation had occurred.

Perforation was accompanied by sudden pain in 21 cases, rigidity was present almost immediately in 7 cases, but it was noted that it was absent or occurred after a lapse of ten hours in 7 cases; decided drop in temperature was noted in only 4 cases, a rise of temperature was the earliest sign in 5 cases; rise in pulse is noted as being marked in 5 cases.

These figures do not represent the frequency of the various signs at all properly, but they do indicate the relative importance of

sudden pain and the fact that rigidity cannot be depended upon as a diagnostic sign.

There is no symptom or group of symptoms that may be depended upon to indicate that perforation has occurred; the sudden abdominal pain is the most frequently present; it may often be masked by the apathetic condition of the patient, and may pass off rapidly; due weight must be given to any reports of the nurse that the patient has cried out with pain, and it must be remembered that such sudden pain often occurs without perforation.

The large number of perforations in this series and the fortunate outcome of six of the operated cases excuses a short digression upon the question of operation. Here the exploratory laparotomy occupies its most honorable place; the hope in the far-off future of saving any large percentage of perforation cases rests in the earliest possible recognition and operation. The early certain recognition is not possible, and the surgeon must operate not when he knows there is perforation, but often when he only suspects it; he must set behind his back his "record" and remember that it requires more courage to operate upon an uncertain than upon a certain case. We must teach on all hands that to open the abdomen when perforation has been suspected and has not occurred, it is to be counted no mistaken judgment on his part, but an indication of honorable zeal —a clear subordination of his own interests to those of the patient. Let it not be replied to this that it is impracticable in "private practice;" naturally it is, but it need not be so in the twenty-first century if the seeds be sown to-day; nor let it be said that if one waits one often finds that the sudden pain and the other symptoms were misleading and the "masterly inactivity" was justified. Such an argument is plausible and misleading. Perhaps there are none of us to-day who is ready to advise operation in all such cases, but it is our duty to teach the triviality of the abdominal section compared with the chances incurred without it.

The Widal Test. The requirements demanded for a positive result have always been strict; a positive reaction requires cessation of movement and clumping, the time limit being from twenty to thirty minutes, the dilution approximately 1:20 to 1:40.

As stated above, the test was present in 92.77 per cent. of all cases tried; in the cases where it was found negative at first and

repeated until positive, the reaction was found in 213 cases to appear upon the 14.7 day of the disease. The earliest day on which it was found present was the fourth day; it did not appear earlier in children than in adults. It appeared in 28 cases (out of 678) on the seventh day, and in 29 cases earlier.

The Urine. Records of the urinary examination are to hand in 575 cases, of which 264 (46 per cent.) showed albumin at some time during the course of the disease; casts were present in 162 (28.2 per cent.), and both together were found in 136 cases (23.6 per cent.) of those examined. The coexistence of these two indicate the presence of a parenchymatous nephritis, but its slightness of degree often does not warrant the use of the term acute nephritis in the sense in which that term is generally understood.

The Ehrlich test (Diazo reaction) was tried in 512 cases, and was present in 344 (67.2 per cent.); unfortunately it was not tried day by day as a routine, but the average of 340 cases shows that it was present on the 11.8 day. It was noticed to have disappeared in 132, on an average of 9.7 days after it was first observed. It reappeared in seven cases, and was present yet a third time in one case.

The Disease in Children. Up to the age of fifteen years 105 cases occurred. Under the age of two years there was one case, a child of thirteen months, in which the diagnosis was confirmed by autopsy.

Duration. Excluding fatal and complicated cases, as well as those where intercurrent relapse was present, the duration of the disease was as follows: 26 cases from one to nine years averaged twenty days; 56 cases from ten to fourteen years averaged twenty-one days.

Stated more particularly the figures are:

Average of	7	cases	from	1	to	5	years	. . . . .	20.3	days.
"	19	"	"	6	to	10	"	. . . . .	20	"
"	6	"	aged	10			"	. . . . .	21	"
"	9	"	"	11			"	. . . . .	19	"
"	10	"	"	12			"	. . . . .	22	"
"	17	"	"	13			"	. . . . .	23.4	"
"	14	"	"	14			"	. . . . .	18.8	"

Degree. Of 31 cases in children up to ten years of age, 27 ran a fever of moderate course (87 per cent.); of 64 cases from ten to fourteen years, the fever was moderate in 54 (84 per cent.).

Symptoms, etc. Of 30 cases under ten years of age, the following were observed :

Rose spots	14	Recrudescence	3
Diarrhea, onset 5, course	7	Hemorrhage	1
Delirium	3	Perforation	1
Bronchitis	8	Albumin in urine	6
Epistaxis	3	Casts in urine	4
Relapse	5		

Of 66 cases from ten to fourteen years (inclusive) the following were noted :

Rose spots	36	Recrudescence	9
Diarrhea, onset 17, course	6	"Steeples"	6
Bronchitis	11	Hemorrhage	2
Delirium	12	Perforation	1
Epistaxis	14	Albumin in urine	8
Relapse	6	Casts in urine	4

Compared with the whole series, the following occurred less often in children : rose spots, hemorrhage, perforation, bronchitis, and albumin and casts in the urine. The following were found oftener in children : delirium, relapse, and recrudescence. It is to be noted that diarrhea and epistaxis were found in children in about the same percentage as throughout the series. A moderate degree of fever is the rule, and the duration is shorter in children.

Treatment. Three courses of treatment have been followed during the period covered by this series : 36 patients received no treatment, 439 cold baths, 94 cold water or alcohol spongings, and 148 antipyretics.

The routine procedure of the baths has been the administration of the first bath at 90° or 85°, second bath 10° lower, third and all succeeding baths at 70° or 75°, always with ice ; duration ten minutes ; cold kept upon the head ; bath administered by two persons rubbing or sponging; whiskey given after the bath if indicated. The bath is given every four hours if temperature is over 102.4°.

Spongings last twenty minutes ; are given between blankets, alcohol or blocks of ice being used.

The antipyretic treatment consists of phenacetin, grs. v, alternating with salol, grs. v; one or the other is given every four hours unless contraindicated ; to this a tepid sponging once or twice daily is added.

It must be understood that these courses of treatment have necessarily varied according to the individual practice of physicians in whose services the cases have been, and that each one may vary his practice from time to time; but a general and concise statement has been attempted.

A brief comparison of methods of treatment is made.

Stated in number of cases:

	Cases.	*Deaths.*	*Hemorrhages.*	*Perforation.*	*Delirium.*	*Bronchitis.*
Baths,	439	48	54	24	67	103
Antipyretics,	148	14	9	10	21	56
Spongings.	94	4	8	4	11	22

Percentages:

	Per ct. of cases.	*Per ct. of deaths.*	*Per ct. of hemorrhages.*	*Per ct. of perforation.*	*Per ct. of delirium.*	*Per ct. of bronchitis.*
Baths,	64.4	72.6	76.0	63.1	67.6	56.9
Antipyretics,	21.7	21.0	12.7	26.3	21.2	30.9
Spongings,	13.8	6.4	11.3	10.5	11.1	12.1

The deduction that the "sponging" treatment is the best of the above is nullified by the fact that the least severe cases are treated by this method; on the other hand, the high percentage of hemorrhages and perforations credited to the "bath treatment" is to be considered along with the fact that this method was used in nearly two-thirds of all cases, and that the number of very severe cases falling to it would consequently be proportionately great. The small number of hemorrhages referable to the antipyretic treatment, and the large number referable to the baths, are indications of the relative height of circulatory strength in a depressant and stimulant treatment, respectively. The relatively high number of cases of delirium in the bath treatment is due, doubtless, to the severity of some cases included, and it is to be remembered that the delirium of to-day is generally little more than mental wandering. The series makes, therefore, no marked distinction in favor of any form of treatment, save that in the bath treatment there are more cases of hemorrhage and neuritis and fewer of bronchitis, whereas in the antipyretic treatment, hemorrhage is comparatively infrequent, and bronchitis moderately frequent. It is difficult to understand why any course of treatment should predispose to bronchitis, and it is likely that the differences are due to season and climate.

Diet. In most cases strictly liquid diet is given, though in a considerable number of cases custard, poached egg, and other semisolids are given even from the first week of the disease. The day on which this kind of food was earliest given is noted in 381 cases. In 73 this was after five weeks, and in 92 it was after defervescence, leaving 216 in which semisolids were given during the disease before normal temperature was reached. In these 216 cases there occurred at different times the following:

Hemorrhage (once immediately after ingestion)	12 times.
Perforation	7 "
Intercurrent relapse	11 "
Relapse	9 "
Recrudescence	20 "
"Steeples"	10 "

These figures are all less than the proportionate numbers in the whole series; but it is to be remembered that the slighter cases only are allowed semisolids. The following facts, too, must be regarded before a decision is made: Of 72 cases in which hemorrhage occurred, the time of giving semisolids was noted in 31; in 12 of these semisolid food was given previous to the occurrence of hemorrhages. In 43 perforations the day of giving semisolids is noted in 7; in all 7 it was given before perforation.

Its Effect upon the Duration of the Disease. The average duration of 185 moderately uncomplicated cases was 23.6 days. Semisolid food was given in the first fourteen days in 125 cases, of which 40 ran a course of twenty-one days or less, 47 ran from twenty-one to twenty-eight days, and 38 over twenty-eight days; 63 cases in which semisolids were given in the first nine days, averaged twenty-seven days. When observing the results of semisolid food it must not be forgotten that milk, if it becomes curdled in the stomach, is practically a semisolid.

The question of food is a vexed one, and no rule will apply to all cases; it may be said that any food which reaches the seat of disease in any other than perfectly fluid form is bad.

A CASE OF GASTRIC SYPHILIS.

By H. A. LAFLEUR, M.D.,
OF MONTREAL, CANADA.

The following case seems to be worth recording for two reasons: 1. The lesion was observed *intra vitam* in the course of an exploratory laparotomy. 2. The patient made a perfect and lasting recovery, up to the moment of writing, a year after the operation:

J. F. L. C., male, aged thirty-nine years, single, came under observation first in June, 1897. In the summer of 1896 he had suffered occasionally from severe pains in the hips and lower extremities, which would last a day and a night and then subside. During the following winter the pains had increased in frequency and severity. He described the pains as aching, with occasional twitches, and worse at night, sometimes preventing him from sleeping. The pains were not increased by walking or other exercise, and would sometimes be absent for a week at a time. He had no difficulty in walking, and did not stagger or stumble. In 1892 he had a sore on the penis, lasting from March 24th to June 1st, and was treated for syphilis by a physician. Very slight, if any, secondary symptoms developed. From that time until the onset of the pains in his limbs he had enjoyed good health. Physical examination, when I first saw him in June, 1897, showed no organic disease of the various organs. Owing to illness I saw him only at long intervals until the end of January 1898, when he again consulted me for the same pains. These had been very severe, occurring every month, sometimes every two weeks, and had not been relieved by full doses of potassium iodid. Eventually, however, the pains subsided gradually, and I did not see him again until November 23, 1901, when he consulted me for indigestion and diarrhea. The latter he attributed to a chill he had got while swimming, at the beginning of September, but he had been failing in health during the summer. The stomach symptoms were flatulency, fulness, and a gnawing feeling in the stomach at all times, but worse after taking food. There was no definite pain and his appetite had remained good, though he dreaded eating on account of the uneasy sensations that followed the ingestion of food. He was also nauseated rather often after food, and occasionally vomited his meal unchanged immediately or soon after eating. The diarrhea was soon

controlled, but the other symptoms were not alleviated by restriction of diet, lavage, or drugs, and throughout November, December, and January he became, if anything, worse. The vomiting particularly became more frequent; nothing seemed to agree with his stomach, but meat seemed to be borne better than any other food. During this time repeated examinations of the stomach-contents were made after a test-meal, and invariably with the same result—an inert gastric juice, containing no hydrochloric acid, no organic acids, and devoid of any digestive action on coagulated albumin. Inflation through the stomach tube showed a prolapsed and dilated stomach, the greater curvature extending below the level of the navel. The stomach washings contained, besides undigested food, small flakes of mucopus occasionally flecked with minute bloody points. As the patient was steadily failing in weight and strength, it was decided, after consultation with Dr. Armstrong, to recommend gastroenterostomy. While not declining an eventual operation, Mr. C. suggested taking a trip to the West Indies, in the hope that the sea voyage and rest would benefit him. He left in February for Jamaica, and was absent two months, during which time his symptoms remained the same and he continued to lose in weight. On his way back he consulted one of the most prominent clinicians in America, who concurred in the advisability of a gastroenterostomy. I saw him soon after his return and was shocked at his appearance. He had lost thirty pounds since the beginning of his illness, and was so weak that the slightest exertion was an effort. There was, however, no distinct cachexia, and the color of the mucous membrane was fairly good. A blood count at this time gave red cells, 5,720,000; white cells, 12,400; hemoglobin, 75 per cent. (Fleischl). Before finally deciding on operation the stomach was again examined, and to my surprise it was found that on full inflation the greater curvature did not extend beyond a point half-way between the xiphoid cartilage and the navel. This seemed to make a gastroenterostomy unnecessary; but it was thought advisable, nevertheless, to make an exploration, find the cause of the trouble, and if possible remedy it. The operation was performed on May 14, 1902, by Dr. Armstrong, and the following account is transcribed almost verbatim from the hospital case-record, omitting only minor details of surgical technic.

Primary incision in midline, midway between the ensiform and navel. Stomach presented—anterior wall held firmly to anterior abdominal wall by thick band of adhesions, half an inch wide and one and a half inch long. This was divided, clamped, and tied. Other denser adhesions were felt below, behind, and above, and prevented extrusion of the organ. The pylorus was found quite free. There was no tumor apparent to the touch, but extending from a point about 2½ inches from the pylorus over toward the cardia the stomach wall felt thicker than normal, and the surface of the organ in this area was characterized by a pinker shade and by scattered shallow puckerings. No glands could be felt in the gastrohepatic omentum or in the hilus of the liver, nor, again, could they be seen in the great omentum. The free

edge of the liver presented a few nodules, which were scraped and found to contain gritty, calcified matter. There being no condition requiring a gastro-enterostomy, it was decided, in view of the abnormal appearance of the anterior wall, to open the stomach and expose the interior. The stomach was opened midway between the lesser and greater curvatures, on its anterior aspect, the incision commencing about 2½ inches from the pylorus. This opened the stomach in the thickened area, and the following condition was found: Stomach wall thick, about 1 cm., in places 1½ cm.; very little bleeding; muscular tissue harder than normal. The everted surface showed complete denudation of the mucosa over an area extending completely around the stomach at the pyloric end of the incision. The same condition extended along the interior and anterior aspect of the stomach toward the cardiac end of the organ fully four inches. Here and there, especially toward the margins of the bared surface, there were small islets of mucous membrane having a rough, cockscomb appearance and a purplish tint. The edges of the ulcerated area were well defined, serpiginous in outline, and abrupt. The edge was slightly heaped up and undermined, and just in the undermining angle was a whitish line. The surface of the ulcerated and denuded area was rather smooth (neither caseous nor necrosing), of a pinkish red color, and almost bloodless. In the thickened area some cicatrization and contracture had occurred, producing a certain degree of hour-glass contracture two or three inches from the pylorus. A slice of mucous membrane, a section through the muscular wall and mucosa, and a snipping from the edge of the ulcer were taken for microscopic examination. After extending the wound to give sufficient space, the exuberant edges of the ulcer were pared, the base was curetted, and the thermocautery lightly applied to as much of the ulcerated surface as could be reached, the very slight bleeding following curetage being easily checked by the same means. The gastric and abdominal wounds were then closed by suture. The subsequent course of the patient's illness was quite uneventful. There was no recurrence of vomiting or gastric distress, and when he left the hospital, on July 3, he was taking a full and varied diet without the slightest discomfort, and gaining weight rapidly. Antisyphilitic treatment was commenced after leaving the hospital, and was continued with intermissions through the summer.

The examination of the tissues removed at the time of the operation was made by Dr. P. G. Woolley, who reported as follows:

"The tissue from the base suggested malignancy, for there were small masses of epithelial cells surrounded by a fibrous stroma; but the edges of the ulcer were simply fibrous tissue and muscle, the former in excess, and there was no marked infiltration. The base was markedly inflammatory, not malignant."

The diagnosis of syphilitic ulceration of the stomach is not one that should be made without careful consideration, or without excluding beyond a doubt the possibility of the more common forms

of solution of continuity; for gastric syphilis is admittedly a rare lesion, and I am quite prepared to admit that the burden of proof still lies with me. Carcinoma, which was at one time suspected, may be at once dismissed. It is not so easy, however, to say unhesitatingly that it was not an *ulcus simplex* of large dimensions, such as have been recorded in the literature from time to time. I would attach some weight to the facts that the patient had not been a chronic dyspeptic, and that anacidity and not hyperacidity existed from the onset of the illness. But the chief argument is drawn from the anatomic character of the lesion. Both Dr. Armstrong, who has had a very considerable experience in the surgical treatment of gastric ulcer, and myself remarked at the time of the operation on the unusual character of the lesion—the soft, redundant, somewhat overhanging borders, the dry and almost bloodless base, and the long, tag-like adhesions on the external surface of the stomach—forming a picture quite unlike that seen in simple ulcer. Macroscopically the lesion was the exact counterpart, save in dimensions, of that described and figured by Dr. Flexner in Vol. XIII. of the TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS as one of syphilitic ulceration. The histologic examination in the present case was necessarily incomplete, only small fragments of tissue being available for microscopic study. It is suggestive, however, that the same masses of epithelial cells surrounded by a fibrous stroma described by Flexner in his case were found by Dr. Woolley in the tissue from the base of the ulcer. As regards evidence of syphilis in the other organs, it is probably not unfair to assume that the nodules in the liver containing gritty, calcified material were the remains of a former gummatous infiltration of that organ. The clinical evidence of an antecedent luetic infection is certainly indisputable.

INFANTILE SCORBUTUS.

By THOMAS MORGAN ROTCH, M.D.,
OF BOSTON.

The following cases of infantile scorbutus of a peculiarly grave type illustrate the necessity of a very careful differential diagnosis from osteosarcoma and osteomyelitis. In one of the cases the subperiosteal hemorrhage especially occurred throughout the whole length of the right tibia. The case closely simulated osteomyelitis. A surgical operation, however, showed it to be hemorrhage. New bone is now rapidly forming, and a complete recovery is expected.

The other case was of an infant nine months old. Extreme swelling and hardness of both femora were found, making a differential diagnosis from osteosarcoma very difficult. Complete recovery followed the administration of orange juice.

Case I.—Daniel C., aged ten months, was sent to the Children's Hospital on February 8th. The family history was negative. He was born at full term. He had been fed on cereal milk, had gained in weight until the present illness began, and had seemed perfectly well.

For two weeks before entering the hospital the right lower leg seemed tender, and four days before entrance a swelling of the right lower leg was noticed. The infant appeared quite ill. He was seen in the Out-patient Department and sent into the house for acute osteomyelitis.

The skin was pale. There was a marked rosary and enlarged epiphyses of both wrists and ankles. There were two lower middle incisors. The gums were slightly reddened about the base of the teeth, but there was no distinct stomatitis ulcerosa. The heart, lungs, and abdomen were negative. The prominent feature of the case was the swelling of the right leg from the knee to the ankle, and this was especially marked above the outer malleolus. This swelling was hard, tense, and tender. The skin over it was glazed, but there was no fluctuation. The rectal temperature was 101° F. The blood showed a count at the time of entrance of 19,200 white cells.

On February 10th the infant was operated upon. An incision was made through the periosteum and a large blood clot found. The periosteum had

been completely dissected from the tibia. A culture taken at the time of the operation was found to be sterile.

On February 18th a second operation was performed on account of the temperature rising to 103° F. The bone was then found to be loose, and the entire shaft of the tibia came out in two pieces.

On February 28th a third operation was performed, as the child was rapidly growing worse. He had run an irregular temperature and had grown pale. There was an ecchymosis the size of a quarter of a dollar below the left nipple. The other leg (left) was at this time in a condition similar to that of the right leg on entrance, except that the thigh was chiefly affected, the swelling extending from the groin to the calf. A complete blood examination was then made, with the following result: Hemoglobin, 50 per cent.; leukocytes, 27,100; erythrocytes, 2,400,000. Differential count of white cells showed: Polymorphonuclear leukocytes, 68.6 per cent.; small lymphocytes, 23.2 per cent.; large lymphocytes, 7.4 per cent.; eosinophiles, none; myelocytes, 0.2 per cent.; mast-cells, 0.6 per cent.

The erythrocytes showed marked poikilocytosis. During the count there were seen normoblasts, 15; megaloblasts, 5, showing a severe secondary anemia.

The operation consisted of an incision through the periosteum of the femur. A large blood clot was discovered and the bone was found to be bare. The child experienced little or no benefit from these operations, but grew steadily worse until March 1st, when the surgeons called me in to see the case in consultation. I suggested the diagnosis of infantile scorbutus, and ordered orange juice. From that time there has been steady improvement in the condition of the child. Additional purpuric spots appeared on March 20th on each side of the neck; on April 6th all tenderness had disappeared, and the periosteal sheaths were firmer, but had not united to the bone epiphyses.

The left leg was still somewhat swollen. The blood count showed a decided change for the better. It was: Hemoglobin, 65 per cent.; leukocytes, 17,800; erythrocytes, 5,080,000. Differential count of 500 cells showed: Polymorphonuclear leukocytes, 67.2 per cent.; small lymphocytes, 21 per cent.; large lymphocytes, 5.8 per cent.; eosinophiles, 6 per cent.

The erythrocytes showed very slight poikilocytosis. During the count there were seen only three normoblasts and no megaloblasts.

The infant's general condition has improved steadily up to the present time. There are evidences of increased bone formation, as shown by the X-ray. The condition of the blood on May 8th was as follows: Hemoglobin, 80 per cent.; whites, 13,700; reds, 5,370,000. A differential count of 400 cells showed: Polymorphonuclear, 37 per cent.; small basophiles, 43 per cent.; large basophiles, 4.2 per cent.; oxyphiles, 12.6 per cent.; myelocytes, 2.3 per cent.; mast-cells, 0.9 per cent.

A stained specimen shows very slight poikilocytosis and achromia, otherwise nothing remarkable was seen concerning the erythrocytes.

This case is presented not only as representing one of the more severe conditions appearing in infantile scorbutus, but also to show how difficult it is at times for the surgeon to differentiate between infantile scorbutus with subperiosteal hemorrhage and osteomyelitis; also, the great value which the use of the X-ray is in such differential diagnosis.

The following reprint from an X-ray taken of a case of infantile scorbutus will illustrate this case. It shows a subperiosteal hemorrhage extending from epiphysis to epiphysis of the left femur, which, with the other scorbutic symptoms, rapidly disappeared on the administration of orange juice.

Case II.—Ambler K., aged nine months, came to the Out-patient Department October 3, 1901. He had been fed for the first five months on Mellen's food, and for the last four months on cereal milk. His birth weight was seven and a-half pounds, and his weight at the time of the first examination was nine pounds, a gain of one and a half pounds in nine months. The family history was negative.

Four weeks previous to being seen he became fretful and irritable, and the lower extremities became sensitive. One week later the left thigh began to swell, then swellings appeared just above the ankles, and a few days later the right thigh became similarly affected. The swelling of the thighs progressed. The mouth was red and sensitive while the baby was cutting two lower incisors.

There was much emaciation. The anterior fontanelle measured 1½ inches. There were two lower incisors. There was a general enlargement of the lymph nodes. The gums showed a slight purplish tinge, but no typical stomatitis ulcerosa. There was a marked rosary. The spleen was just palpable, and the liver was palpable two fingers' breadth below the costal border. The prominent feature of the case was the marked enlargement of the thighs, in contrast to the emaciated body, especially the arms. The swellings extended from epiphysis to epiphysis, being especially prominent anteriorly. There was no limitation of motion in the joints. The swellings were apparently connected with the bone, were hard and tense, and somewhat tender, but showed no heat or redness. There was no edema of the subcutaneous tissue. Above the left inner malleolus was a similar swelling, much less advanced. The blood showed 7400 leukocytes. There was no pronounced pallor.

The right thigh measured 8¼ inches. The left thigh measured 7⅛ inches. The treatment consisted of cow's milk, properly modified, and orange juice.

Subsequent History. There was considerable difficulty in adjusting the food to the infant's digestion, but the swelling and tenderness of the legs rapidly diminished in spite of the persistence of more or less indigestion. At the end of four weeks each thigh had diminished nearly two inches in cir-

Case I. Infantile scorbutus.

Case II. Infantile scorbutus.

cumference, and there remained no evidence of any swelling or tenderness. The weight was still nine pounds, but from that time the baby began to gain on the following modification of milk: Fat, 2.50; sugar, 6.00; proteids, 1.00; alkalinity, 15.00; 10 ounces barley-water in a 40-ounce mixture; six feedings of 6 ounces gradually increased to 8 ounces. In seven weeks the baby had gained three and three-fourths pounds. The food was then rapidly increased in strength and quantity, and in the following March, four and a half months after the beginning of the treatment, the weight was seventeen pounds, a gain of nine pounds.

The history just given was that of an advanced case of infantile scorbutus. There were certain points in the case, however, which are of great significance. In the first place, before the treatment was begun the right thigh not only showed considerable enlargement, but was hard and dense, unyielding to pressure, and was so hard that it strongly suggested the presence of osteosarcoma. The case, therefore, was a difficult one in which to make a differential diagnosis, and it had even been suggested by some who saw the patient that an amputation for osteosarcoma would be needed. It is presented as a condition which, without the use of the X-ray and with the absence of other symptoms of scorbutus and apparent lesions in the other limbs which may occur in infantile scorbutus, would make the differential diagnosis between osteosarcoma and subperiosteal hemorrhage very difficult.

DISCUSSION.

DR. JACOBI: In what condition was the bone; why was the operation required?

DR. ROTCH: There was complete disorganization, with large sequestrum.

DR. JACOBI: Did that condition precede the scorbutus?

DR. ROTCH: No; it had the general symptoms of infantile scorbutus. There was subperiosteal hemorrhage and the bone was disorganized.

DERMATOMYOSITIS

By F. FORCHHEIMER, M.D.,
OF CINCINNATI, OHIO.

This form of myositis was unknown as a clinical entity until 1887, when Unverricht called attention to it as polymyositis progressiva acuta, which name he changed to dermatomyositis acuta in 1891. Before Unverricht's first publication E. Wagner (1883) had recorded a case under the title of "A Case of Rare Muscular Disease," and Potain (1875) another with the diagnosis of chronic glanders. In 1887 E. Wagner published the account of another case under polymyositis acuta, and Hepp one with the diagnosis of pseudotrichinosis. The designation which forms the title of the paper is the one universally accepted, except Lépine, of Lyons, has called the disease angiomyositis. The history of the case, which I believe to be a case of dermatomyositis, is as follows :

Mrs. A. B., aged forty years; family history negative as to tuberculosis, syphilis, gout, and rheumatism, but markedly neurotic. The antecedent history is that of a very neurotic woman; she has had much headache; married at twenty-five; she has had two children, whose rearing has given her much anxiety, increasing her neurotic tendencies. She was thrown out of a pony-cart, striking upon her head, and had cerebral concussion, which was followed by a very sharp attack of traumatic neurasthenia. In June, 1901, when partially recovered, the sudden death of her brother produced great worry, care, and anxiety, which caused her to use up all the little reserve nerve force that had been stored up, and from this time on she has not been well. She began to complain of irritation of the skin, of the mucous membrane of the vagina and rectum, of irregular menstruation, scant and offensive urination, constipation, headache, and pain in various parts of the body.

August 20, 1901, she noticed a small pustule on the left leg where the garter had pressed, accompanied by itching and muscular soreness, but no swelling. September 8, 1901, her general condition being as noted before, she noticed itching over the left gluteal mass, which was accompanied by an

erythematous eruption and the formation of a pustule; she cannot state which appeared first. September 10–12, 1901, three lesions of the same nature developed in the ischiorectal region, and, fearing an ischiorectal abscess, she was intrusted to the care of my colleague, Dr. P. S. Conner, who opened the pustules, and finally made a deep incision, giving no relief and finding no pus. There now was a cessation of local symptoms for two weeks, which returned in the ischiorectal region, in the form of deep swellings, which were repeatedly incised without result, and, her general condition becoming so bad that she had to go to bed, I was again called in. I found her in the following condition: The patient was emaciated, weak, very nervous, depressed; temperature, 102° F.; pulse, 110, small, and occasionally irregular. There was an erythematous rash upon her face; the eyelids and the whole region around the eyes were very puffy; the rash extended over the neck, chest, and back. The internal organs were normal, except that the spleen was enlarged, being felt below the free border of the ribs. During the next twenty-four hours she passed 900 c.c. of urine; specific gravity, 1015; no abnormal constituents, and non-toxic. A blood examination gave the following: Red corpuscles, 4,102,000; white corpuscles, 5200; hemoglobin, 6.72 per cent. (Fleischl); polymorphonuclear cells, 79 per cent.; small lymphocytes, 18 per cent.; large lymphocytes, 2.5 per cent.; eosinophiles, 0.5 per cent.; no poikilocytosis; no nucleated red cells. About this time there appeared upon the right leg a condition characterized by the following appearances: The skin over the lower end of the peroneus brevis was edematous; the edema was hard; it did not extend beyond the ankle. Motion produced great pain, as did also pressure, especially at the insertion of the tendon. There was no pain in the joint, and the nerves were not sensitive to pressure. There was no pain at all when the leg was kept perfectly quiet. All the reflexes were normal.

The next day, October 21, 1901, the hard edema has spread; there is also evidence of a small pustule over the place first affected, which was again incised, but with no result.

24*th*. Another lesion, the same as the one just described, appears upon the left leg, with the same results.

28*th*. The same condition is noticed upon the right thigh, but as the edema is not so well marked, I find that the rectus muscle is swollen, almost simulating fluctuation, but hard, over an area as large as the palm of my hand. The patient complains of pain in breathing, which is found to be due to an inflammatory condition in the intercostal muscles, which are found to be very painful upon pressure. The edema extends over the abdomen to the lower thoracic region. During all this time the general condition of the patient goes from bad to worse: the fever continues as a remittent fever, ranging from 100° to 102°; the pulse rapid, somewhat out of ratio with the temperature and more irregular, and the general appearance of the patient indicates a much more serious condition than is warranted by the local symptoms.

29*th*. Another lesion has developed upon the right thigh, and to-day the general condition becomes still worse; more or less general hyperesthesia, sleeplessness, severe headaches, total loss of appetite, and great depression; temperature is normal; pulse from 96 to 108; the local condition stationary except in that the edema is disappearing. During the last week furfuraceous desquamation is taking place over all the parts that have been affected by the skin process, leaving pigmentation of the skin, which never disappears entirely.

November 5*th*. The pulse is now 75 to 84. The muscular symptoms persist, and there is some improvement in the general condition.

8*th*. The last local manifestation presents itself in the form of an urticarial rash upon the left leg and thigh. From this time on there was a gradual improvement of local symptoms. Generally there is a return of the neurasthenic condition. There was a constant struggle to feed the patient. This could only be done by liquid food, and although she received at least 3000 c.c. of liquid food daily, the quantity of urine never went above 2000 c.c., the average being 1400 c.c., nothing abnormal being found in it, and several additional tests for toxicity proving negative. The bowels during the whole course of the disease were constipated. There was much flatus, and when the bowels were moved by artificial means the result was always a small, scybalous mass, extremely dry and very offensive. Repeated blood examinations showed about the same condition as noticed before. For obvious reasons neither microscopic nor electric examinations could be made, but electric examinations made during convalescence and at the time of writing show conclusively that the muscles which had been affected are atrophied. There is no reaction to either galvanic or faradic current. It is of interest to note that on November 3, 1901, inunctions of Credé's ointment were begun, and that the local manifestations of the disease disappeared two days afterward.

The convalescence was extremely slow, and it was only in the fall of 1902 that she had gained fifteen pounds and was able to walk about with any comfort. An examination on March 20, 1903, shows pigmentation about the face, but to a much less degree than before; the muscles affected are still slightly tender upon pressure and motion. The patient states that movements requiring special efforts of the muscles affected are carried out very clumsily. She states that in mounting her horse she finds her former elasticity is gone, and that she requires an unusual amount of assistance in mounting and dismounting.

At the present time, in view of the publications of Pfeiffer and of Lorenz, it is necessary to demonstrate that this case is one of dermatomyositis, for in 1893 Lewy reported twenty cases of this disease, which at the hands of Pfeiffer (1896) were reduced to twelve, although two cases apparently characteristic (Herz and Fränkel) had been reported in the meantime; and Lorenz (1898) is willing to add only three more to Pfeiffer's list; this, notwith-

standing the fact that nearly thirty cases have been reported under the various titles of polymyositis progressiva acuta, polymyositis acuta or dermatomyositis before Pfeiffer's publication, and four more up to the date of Lorenz's article. Unverricht (1887), who first described the disease as polymyositis progressiva acuta, changed this name to dermatomyositis (1891), because a case reported by Plehn showed that the disease was not progressive, as far as a fatal termination was concerned, and also because he wanted to give prominence to the lesions in the skin. Lorenz does not accept this case, so inflexible are his diagnostic requirements, but puts it into another class of muscular diseases. There is no doubt but that the classification of cases reported as dermatomyositis requires great care ; but, on the other hand, there are certain criteria which are sufficient to establish the fact that an individual case belongs to this class.

Unverricht defines the disease as one characterized by fever, enlargement of the spleen, edema, acute marked inflammatory condition of the muscles, especially of the extremities, with extension to the muscles of respiration and deglutition, not affecting those of the eyes, the tongue, and the diaphragm, and an eruption presenting the appearance of an urticaria-like or erysipeloid eruption. In his second paper he adds hemorrhagic eruptions as of special importance, because of their constancy. If we compare this with Pfeiffer, we find an essential agreement ; he adds that the diagnosis is easy when Unverricht's description is followed, and that, for the present, chronic and abortive forms must not be accepted. Lorenz adds the following in his general description : There is usually a prodromal period of several days, malaise, rheumatoid pains, and with these an ascending type of fever to 40° C. ; then the symptoms on the part of the skin, cellular tissue and muscles; the edema usually beginning upon the face, especially on the eyelids ; usually enlarged spleen ; constantly profuse sweats. The disease attacks a large number of the muscles of the body; in most of the cases the muscles of the trunk are implicated (intercostal muscles and diaphragm) and in many cases those of the larynx and pharynx. In a few cases the muscles of deglutition and respiration are not affected, or there may be improvement in the existing affection of these muscles when the patients do not die.

He has added to Unverricht's description the prodromal period, the sudden onset with fever, the beginning of the process as far as the skin is concerned upon the face (*"gewöhnlich"*), the constancy of profuse sweats, and the involvement of a large part of the muscular apparatus, not especially of the extremities, and the eruption, not so limited as to character. If we compare the symptoms of Unverricht and Lorenz we find that the latter, having a greater number of cases from which he could generalize, has extended the clinical picture ; but, upon the whole, the diagnosis of the disease would have to be determined by the cardinal symptoms—those on the part of the skin, the muscles, the connective tissue, and the general symptoms. On the part of the skin we have the eruption and the sweats ; the edema is an inflammatory edema; the muscles are swollen, painful to the touch and upon motion; the general symptoms are fever, enlarged spleen, those due to affections consecutive upon the involvement of muscles in various parts of the body. The onset of the disease may be very gradual or very sudden; the course of the disease may be acute, subacute, or chronic. Of these symptoms, fever is most commonly present, as well as the symptoms on the part of the skin, the connective tissues, and the muscles. Yet Unverricht reports a case in which only the three latter groups of symptoms were present. This is reported tentatively by himself, and is accepted fully by Lorenz, although fever, sweats, and an enlarged spleen are absent, as well as the characteristic eruption of Unverricht.

If we now analyze the case presented we will find as follows: It is difficult to determine when the beginning of the disease occurred, as the patient did not come under my observation until there was inflammation of muscle and of skin (August 20, 1901). According to her own account there were prodromal symptoms before the first onset, and a cessation of all symptoms before the second onset of the disease. This second onset was, in my opinion, characteristic of the disease in that there were present symptoms on the part of the skin, the connective tissues, the muscles, and general symptoms. The skin symptoms were erythema, pustules, and urticaria ; they began, as they do in a large number of cases, about the face, involving the eyelids. The muscles of the thighs, legs, and the intercostal muscles were affected. The edema was the character-

istic edema, and extended over the affected parts and over the abdomen and lower thoracic region. The general symptoms were fever, enlarged spleen, increased pulse rate, depression, and symptoms on the part of the urinary and digestive apparatus. The lesions of the skin led to pigmentation, as in Löwenfeld's case. The inflammation of the muscles led to atrophy. The disease lasted two and a half months, and the convalescence was very slow. The exceptional conditions in this case may be noted as follows: If we consider the beginning of the disease from August 20th we will have to look at its complete outbreak as a relapse, which does occur in this disease. The first onset which, at best, can be looked upon as belonging to the abortive type, may also have been the cause of the second attack. As to the existence of abortive attacks, we have already seen what Pfeiffer says upon the subject, and as applied to this case I should certainly hesitate to call it one, in that there were symptoms only on the part of the skin, rudimentary affection of the muscles, and no edema. Yet it is impossible to decide this question, if we accept rudimentary forms at all. If we reject this form, then the solution is easily arrived at, but this would be in direct opposition to the knowledge derived from our observation of other diseases, in that we find abortive forms in all diseases. The skin symptoms were somewhat different from those of any of the cases reported, in that there were found pustules; this could not be looked upon as militating against the diagnosis, as in one of Oppenheim's cases there were ulcers. There were also no sweats; on the contrary, the skin was constantly dry, so much so that the patient complained of it. Lorenz, in ascribing a constancy to this symptom, overestimates their frequency in saying they are constant, in that they are only found in eight of his fifteen cases. There were also symptoms on the part of the heart; this was a neurosis, as the patient had at times suffered with the same condition long before she had her dermatomyositis, and except on direct provocation she has been free from it since. But even if it had been an organic disease it would not affect the diagnosis, as Potain's case had a fresh endocarditis, and it is no longer accepted that the muscle of the heart remains unaffected (Pfeiffer).

In a number of cases (Senator) the pulse temperature ratio was found as in the case reported. Depression and sleeplessness have

also been reported (Wagner, Hepp, Potain). Disturbances of the gastrointestinal tract also are accepted (Unverricht), but not much stress is laid upon this condition. One of Senator's cases had an attack of botulism from eating spoiled crabs, but in none of the recorded cases do I find so much persistent trouble as my patient had. In no other case was there noted oliguria as was found in the one reported. On the day the patient's blood was examined she passed 900 c.c. of urine, with low specific gravity (1015), and the specific gravity of the blood (chloroform-benzine mixture) was 1033; this was not due to the low quantity of hemoglobin, which was 70 per cent., as with a specific gravity of 1038 of the blood the hemoglobin ought not to exceed 35 per cent. In this case there was a remarkable retention of fluid in the blood, which was not excreted either by the kidneys, the skin, or the bowels; how much was exhaled it was impossible to determine. We have, then, in this case all the typical symptoms of dermatomyositis present, beside those especially noted, and with this the diagnosis seems clear, as, for the present, the disease must simply be looked upon as a syndrome —at least this must be the case until the etiology has been worked out. Many things have been accused of producing this disease: botulism and intestinal autoinfection (Senator); in four cases there was found tuberculosis (Strümpell), CO poisoning (Litten), gregarines (Unverricht, Strümpell, Köster) which have never been found, overexertion (Löwenfeld), toxemias and infections (Hepp), and, finally, vasomotor disturbances due to some unknown cause (Köster). In one case (Fränkel) there was a septicopyemia from a purulent otitis media; it is sufficiently characteristic to be classed with dermatomyositis. Nearly all authors reject it (Bonnet, Pfeiffer, Lorenz) because it is manifestly due to sepsis, yet Senator accepts it as dermatomyositis, but prefers to have it called a secondary dermatomyositis. The septic origin of this disease is strengthened by the occurrence of amygdalitis (Hepp) and stomatitis (Strümpell) as a possible source of infection, but yet in the majority of cases, as in the one here reported, the clinical picture varies very much from the average case of septicopyemia. The only possibility of this case being looked upon as a sepsis would be the one that before the intermission of symptoms there was an infection from the skin; on the other hand, the skin lesion—that is, the pustules—was

present in the recrudescence of the affection. Köster's hypothesis is very seductive, and many things in the case reported point to the existence of serious vasomotor disturbance. Indeed, part of the manifestations of the skin are comparable with the conditions found in angioneurotic edema and others with those in scleroderma. If anything at all has been shown as to etiology it is that apparently the disease may be produced by a number of causes. Until these are worked out we can only rely upon symptomatology for diagnosis, and the symptoms are being added to with the increase in the number of cases reported. But it seems to me premature to accept the diagnosis unless there are present sufficient characteristic symptoms. The clinical picture of a case of dermatomyositis, when typical, is one not to be forgotten, and the diagnosis is easy only when it is typical and when one has already seen a case.

Bibliography.

Bonnet. La Dermatomyosite aïgue. Gaz. des Hôp., April, 1900.

Fränkel, A. Ueber eigenartig verlaufene septicopyaemischen Erkrankungen, etc. Deutsche med. Woch., 1894, pp. 9, 10, 11. Also discussion Berl. klin. Woch., 1894, p. 877.

Hepp. Ueber Pseudotrichinose, eine, besondere Form von acuter parenchymatöser Polymyositis. Berl. klin. Woch., 1887.

Herz. Ueber gutartige Falle von Dermatomyositis. Deutsche med. Woch., 1894, p. 41.

Jacoby, G. W. Subacute Progressive Polymyositis. Journal of Nervous and Mental Disease 1888.

Köster. Ueber primare Dermatomyositis I. Monatshefte f. prakt. Dermatol., 1899, p. 1651. II. Monatshefte f. prakt. Dermatol., 1898, p. 1594.

Lewy. Zur Lehre von der acuten primaren Polymyositis. Berl. klin. Woch., 1893, pp. 8, 9, 20.

Lorenz. Dermato-myositis. Nothnagel, vol. xi., iii. p. 160.

Lowenfeld. Ueber einen Fall von Polymyositis acuta. Münch. med. Woch., 1890, pp. 31, 32.

Milet. L'Angiomyosite. Thèse de Lyon, 1893.

Oppenheim, H. Dermatomyositis. Berl. klin. Woch., 1899, p. 37.

Pfeiffer, Rich. Die Polymyositis, respective Dermatomyositis acuta. Centralbl. f. allg. Path. u. path. Anat., 1896, No. 3.

Plehn. Ein neuer Fall von Polymyositis acuta mit Ausgang in Heilung. Deutsche med. Woch., 1889, No. 12.

Potain. Morve chronique de forme anomale. Bul. de la Soc. méd. des Hôp. de Paris, 1875.

Senator. Ueber acuta Polymyositis und Neuromyositis. Deutsche med. Woch., 1893.

Strümpell. Zur Kenntniss der acuten primaren Polymyositis. Deutsche Ztschr. f. Nervenh., 1891, p. 2.

Unverricht. Polymyositis acuta progressiva. Ztschr. f. klin. Med., 1887, p. 12. Dermatomyositis acuta. Deutsche med. Woch., 1891, p. 2.

Wagner, E. Fall einer selteren Muskelkrankheit. Archiv f. Heilkunde, 1863, p. 4. Ein Fall von acuter Polymyositis. Deutsches Archiv f. klin. Med., 1887, p. 40.

STUDIES UPON THE CAPSULE OF THE KIDNEY.

By HAVEN EMERSON, M.D.,
OF NEW YORK.

Presented by S. J. MELTZER, M.D.,
OF NEW YORK.

INTRODUCTION.

In the course of studies upon the capsules of various organs the following observations were made upon the capsules of kidneys in dogs and rabbits:

In Part I., I offer observations upon the immediate and later effects of experimental decapsulation of the kidney in dogs and rabbits. In Part II. the report is based upon the experiments devised to test the function of the capsule of the kidney in its relation to absorption.

Part I.

The results of decapsulation were observed upon twenty dogs and three rabbits. Of the dogs fifteen were observed for one-half to three hours after decapsulation, then used for other purposes and killed; five were operated upon under aseptic precautions, and three of these were autopsied thirty-nine to two hundred days later. Two of the rabbits were autopsied fifty-nine and eighty-four days later.

The hemorrhage resulting from stripping the healthy capsule in the dog ceases in about five minutes, the kidney surface being soon after covered with clear lymph, which, at the end of half an hour, makes a homogeneous, jelly-like coat. This gradually becomes cloudy, and at the end of two hours appears quite opaque by the formation of a dense fibrin network—*i. e.*, a continuous lymph clot covers the denuded renal surface.

For the later results of the decapsulation I offer the following reports of autopsies. All the animals operated upon recovered without urinary or constitutional symptoms, and were in perfect condition at time of autopsy.

CASE I.—Mongrel adult male, 10.5 kilos, thirty-nine days after decapsulation of the right kidney. Adhesion to the left lobe of the liver about one-half inch long; also to the omentum, the latter not only over the decapsulated area, but at the hilus as well, where only the peritoneum had been stripped. But slight bleeding occurred on separating adhesions, and this apparently wholly from the liver side and none from the kidney, the animal being kept under ether for an hour to study the circulation; the newly formed covering of the kidney more adherent than normal, though quite soft and tearing the parenchyma slightly when stripped.

Microscopic (Müller's and formalin 5 per cent. solution for hardening and hematoxylin-eosin for staining). Normal kidney shows an even capsule and inner, thinner cellular layer, and an outer, thicker, fibrous connective tissue layer. The operated kidney shows newly formed connective tissue envelope, in some places thinner, elsewhere from three to five times thicker than normal. The outer layer has abundant round cells loosely embedded in young connective tissue. The inner layer still marked, evidently not stripped off at operation, but its identity much less at the site of adhesions, where it appears absorbed, and where occasional wedges of round cells are seen crowding between urinary tubules. The whole newly formed coat appears but slightly vascular; no changes appear in the renal parenchyma.

CASE II.—Adult male fox-terrier, 8 kilos. Examined one hundred and forty-four days after decapsulation of the right kidney. Firm adhesions between the right kidney and left lobe of the liver, pancreas, mesentery, and large intestine. Marked absence of bleeding from tearing attachments, except where the pancreas is attached so closely that it cannot be separated without tearing off the newly formed capsule. The surface of the kidney is irregular, appearing like the granular kidney seen in chronic interstitial nephritis in man. The capsule cannot be removed without tearing the parenchyma.

Microscopic examination shows essentially the same variation from normal as Case I., with the following differences:

The inner capsular layer strikingly absent where adhesions are formed, and especially at the site of pancreatic attachment; elsewhere the inner layer is thicker than normal. The outer layer and capsule, as a whole, are everywhere much thickened. The small, newly formed vessels are seen in the loosely arranged connective tissue bundles between the pancreas and kidney. Tubules which come to the surface are in places distorted and crowded by the encroachment of connective tissue cells; but, aside from this, no increase of intertubular network is apparent.

CASE III.—Small male, mongrel puppy, 5 kilos. Examined two hundred

days after decapsulation of the right kidney. Adhesions to the pancreas, liver, and posterior abdominal wall almost cover the kidney surface. The viscera are connected, not by bands, but directly surface to surface. The muscular attachment is by a dense non-vascular band, impossible of separation without tearing off the newly made capsule and some of the renal parenchyma. This kidney was then injected with gelatin mass. The attached parts of the liver and pancreas were cut off with the kidney, the renal artery and vein canulized, and the kidney washed out with normal saline solution; then thin gelatin, deeply stained with Berlin blue, was injected at a temperature of 98° to 100° F. and 180 to 200 mm. mercury pressure for one-half an hour by the artery and one-half an hour by the vein. From the cut surfaces of the pancreas and the liver the blue mass flowed freely during the whole period of injection. The specimen was then chilled, hardened in Müller's and formalin, sectioned, and stained as before.

Microscopic examination shows the following:

(*a*) The section where no adhesions were formed shows a much thickened capsule of new, dense connective tissue, with small bloodvessels injected with the blue gelatin mass directly connected with the capillaries of the renal parenchyma. Deep wedges of round connective tissue cells enter from the capsule as far as the glomeruli nearest the surface.

(*b*) The section where the liver is in intimate contact with the kidney shows in some places a thin layer of dense connective tissue of the thickness of the inner layer of the normal capsule, and no vessels communicating between the two viscera. In other places is seen marked injection of liver capillaries and injected vessels in the connective tissue between the two viscera. At some points there are but two extremely thin layers of very flat connective tissue cells separating the viscera from each other. At frequent places along the renal cortex are seen deep connective tissue wedges distorting, destroying, and occluding the tubules, and in some instances even completely surrounding glomeruli.

(*c*) Where the pancreas is adherent to the kidney the connective tissue separating them is thicker than in the case of the liver; otherwise the conditions are the same. Blue injection mass is seen in the smaller vessels and capillaries at various points in the pancreas.

Case IV.—Brown and white buck rabbit, autopsied fifty-nine days after operation.

Case V.—Slightly larger brown and white buck rabbit, eighty-four days after operation. The gross appearances are identical in both, there being no adhesions to other viscera, as the operation was wholly extraperitoneal—a procedure impracticable in a dog. Perirenal fat is more firmly bound to the operated than to the normal kidney. A slight milkiness and perceptible difficulty in stripping the newly formed capsule were all that distinguished the operated from the normal kidney.

Microscopic examination of Case IV. shows the layers of the normal capsule less marked than in the dog. The newly formed capsule presents the

characteristics of young connective tissue. It is thicker by four or five diameters than normal. Round cells are abundant throughout, no vascular connections with the parenchyma are found, and no infiltration of the parenchyma with connective tissue cells. The new capsule has formed under the intimately attached perirenal fat.

Microscopic examination of Case V. shows exactly the same state of things, except that the newly formed outer layer is denser and the cellular elements less marked.

The conclusions from the preceding observations may be summed up as follows:

Stripping the capsule of the normal rabbit kidney retroperitoneally results in prompt formation of a dense connective tissue coat, no interference with the parenchyma, and apparently no new vascular connections between the new capsule and adjacent structures.

Stripping the capsule of the normal kidney of the dog results in the formation of a dense connective tissue coat, with more or less intimate adhesions with the visceral and peritoneal folds, the site of closest visceral adhesions showing absorption of the new connective tissue coat and the establishment of vascular connections from the kidney to the new capsule, and from the new capsule to adherent viscera. In the cases observed longest there is apparent a beginning interstitial increase from the kidney surface encroaching upon the parenchyma with destructive effect and making an uneven renal surface.

From the point of view of the practising physician the conclusions would arrange themselves as follows:

Where decapsulation is done extraperitoneally, as in the rabbit, the kidney, surrounded by fatty tissue, does not form any new vascular connections, nor is there any new connective tissue increase in the parenchyma.

On the other hand, in the dog, where the decapsulation is intraperitoneal, we have marked vascular connection with important viscera, not with fatty tissue, and so marked a formation of connective tissue penetrating the parenchyma from the new capsule as to present the picture of a beginning interstitial (or diffuse) nephritis.

Where we find vascular connections we see the most serious lesions of the renal parenchyma. Where the renal lesions are not found we see no formation of new blood channels.

Part II.

In the hope of determining the functional significance of the capsule of the kidney, the major part of this research was undertaken, and the following brief report summarizes the findings to date:

The tests of the absorptive power of the kidney of the dog, with and without its capsule, were made briefly in the following manner:

After abdominal incision the ureters were catheterized, one kidney freed from peritoneum and fat and enclosed in a thin, rubber-tissue bag, applied so as to be water-tight without congesting the organ. Solutions were then put into the bag by a glass tube tied into the blind end. After washing with saline solution until all bleeding ceased, the test solution to the amount of 50 c.c. was put into the bag and the urine examined at frequent intervals.

Solutions of potassium iodid, 1 per cent. to 10 per cent., were applied for periods of one-half to two hours to the kidney, with the capsule intact, and in no case was iodin found in the urine.

The same solutions were applied to freshly decapsulated kidneys, and iodin was found in the urine in twenty minutes.

Sodium salicylate in 10 per cent. solution was applied with the same results, except that in the case of decapsulated kidneys the test did not appear for twenty-five minutes, and the secretion of urine was distinctly diminished.

Potassium ferrocyanid in 10 per cent. solution gave the same results, but the test did not appear in the urine until forty-five minutes had passed. The test with potassium iodid was made also in Cases I. and II., above described in Part I., and the newly formed capsules, thirty-nine and one hundred and forty-four days old, respectively, were found to prevent absorption, as does the normal capsule.

Conclusion. The conclusion to be reached by this brief series of tests is that the normal capsule of the dog's kidney serves the function of preventing the absorption directly through its substance of fluids in which it may be bathed, whereas when the capsule is removed, for a short time after, absorption of fluids may occur into the blood stream through the parenchyma.

SKIN LESIONS ASSOCIATED WITH RAPID GROWTH OF LONG BONES—LINEÆ ALBICANTES (LES VERGETURES DE CROISSANCE, JULES COMBY).

By W. P. NORTHRUP, M.D.,
OF NEW YORK CITY.

For some years I have had in mind the scars across the knee here shown in the photograph. I could never explain the scars of my early patient; I had never seen any like them, and in several years of subsequent hospital observation I have not added a similar case to my experience. They come under the names of lineæ albicantes, lineæ atrophicæ, etc., and are very similar to those on the parturient woman's abdomen. I incline to the belief that this particular lesion, or this particular locality of lesion, is not common.

Last summer I picked up in Paris a new edition of Jules Comby's book on *Children's Diseases*. In looking it through I came upon a chapter, "Maladies of Growth." Here I found described exactly the case under consideration. The lesion figured in the photographs pertains to an adult male, in the neighborhood of perhaps rather more than six feet.

His case is as follows: He belongs to a tall family, but the patient is two inches taller than any of the others—father or brothers. At the age of seventeen years the patient was rather below the average size, wore size 12 collars, gloves of ladies' size. At seventeen he contracted typhoid fever, was very sick, in bed six weeks; his life, he was told, was despaired of for five days. When he first stood up he was said to have grown in height. For two years he heard frequently the exclamation "How he grows!" Those who had not seen him for two weeks declared he had grown perceptibly. A chum of his of nearly equal size

before his illness, could within three years stand under his outstretched arm. He is sure of this, because they were both in the same circle of friends, and the experiment was often tried. The fact of unusual and exaggerated growth seems established. He remembers his illness thoroughly, that he was greatly emaciated, that his knees were never swollen, that his feet were swollen when he began walking out-of-doors, but not his knees.

As to the scars across his knees, he feels sure they were not there during the beginning of convalescence, and cannot recall when they first appeared. When first seen they were pinkish, like wales or welts made by a switch. Does not recall whether they were raised any more than at present. There are no other similar scars on his limbs or body.

The elements of this case are summed up in Jules Comby's[1] book, and I have never seen so full an account elsewhere:

"All acute and chronic illnesses, febrile or apyretic, which condemn a child whose growth is not yet terminated, during a long time to horizontal rest, has for habitual result very remarkable growth in height. A child which presents each year an average growth of 5 cm. often passes this limit in some weeks, under the influence of a typhoid fever, for example. An elongation of the long bones is so rapid in such cases that the development of the skin is not able to keep pace, and there results frayings (éraillures), wales, welts (vergetures), the habitual location of which corresponds to the femorotibial regions. The accession of growth is explained by the horizontal position, which results in annulling the reciprocal pressure of the bones and by the irritative congestion of the bony marrow which typhoid fever generally produces" (p. 267).

Under Typhoid Fever, he speaks of a girl of thirteen years who suffered several relapses of typhoid fever, who was in bed four months, recovered with rapid growth and pronounced welts (belles vergetures), p. 113.

"It is not rare to see a child present as a result of typhoid fever a rapid and excessive growth. Such growth shows itself sometimes besides elongation of the skeleton, by cutaneous welts (vergetures), having for their location the knees, and may occupy also other parts of the body."

[1] Maladies de Croissance. Traité des Maladies de l'Enfance. Fourth edition, Paris, 1902.

In talking with friends I have been able to find one case similar to that here shown. I am indebted to Dr. Charles Norris for the following:

A girl, thirteen years old, in the summer of 1878 suffered a prolonged attack of typhoid. The doctor's account of the vergetures is as follows:

"The scars have irregularly edged borders. The epithelium which covers them is glistening or glazed, or porcelain-like in appearance. They vary in length, one to three inches, in breadth one-quarter inch or more, in places. Over the dorsal surface of both knees I should say there were at least fifteen to twenty scars, which are slightly curved, arranged in more or less parallel rows and run at right angles to the length of the bones. They are found only over or just above the knees. A few smaller and less conspicuous scars are found over the back of the upper arm just above the bend of the elbow, more marked over the right than the left arm. They also are parallel, one just above the other, three or four in number. The lesions appeared as large, intensely reddish or bluish welts, raised above the surface. Apparently they remained stationary for a number of years, the evolution into the present whitish flat scar having been a very gradual one. When going out into society the scars were somewhat a source of annoyance, as they, on account of the reddish color, showed through thin sleeves. Evidently they were reddish five or ten years after recovery from the disease. Neither the patient nor friends are quite sure when—that is, how long after or during convalescence—they made their appearance; but it seems more than likely that they were noticed some time during the convalescence, which was a protracted one. The location of the scars exclusively over the epiphysis of the long bones, seems to confirm the explanation which M. Jules Comby offers."

Hare, in the *Medical Complications of Typhoid Fever*, p. 249, says: "A somewhat unusual lesion of the skin resulting from typhoid fever is the development of lineæ albicantes." It is stated that they occur most frequently in children and young adults. Bucquoy notes that in boys these whitish lines have no special areas of distribution; but in girls, the breasts and crests of the ilium are the places where they usually appear.

Barié has reported the case of a girl, aged seventeen years, in whom these lines appeared over the knuckle-joints of each hand.

A somewhat similar condition, due to localized atrophy of the skin, is recorded by Bradshaw. In his case, a girl of thirteen years, who had suffered from typhoid fever followed by relapse, and again by a second relapse, finally developed, during convalescence, upon the inner surface of the lower one-third of the thigh, a number of horizontal markings, some of which practically surrounded the limb. They were about one-half inch in width, regular in contour, and almost exactly alike on both legs.

The skin lesions in the case photographed (les vergetures) are located as the patient stands over the patella, and just above. They are symmetrical. When the knees are flexed at right angles the scars ride up with the skin and are distributed over the lower end of the shaft, epiphysis, and patella, on the extensor and lateral surfaces, rather more marked on the inner surfaces. There are none on other skin surfaces of the body. Patient does not remember when they first appeared. They were first pinkish, later porcelain-white. The scars are about a line in width, irregular zig-zags running together, twenty to fifty on each knee. They are in every way similar in appearance to the lineæ albicantes of the parturient woman's abdomen.

The same causes which make frayings of the skin in the rapidly growing abdomen of the pregnant woman may act in a similar way in the rapidly elongating long bones of the leg in the particular combination of youth, typhoid fever stimulating to exaggerated growth of bone and enforced horizontal rest, literally. It would seem that the skin cannot keep pace with the bones and fraying results.

The photographs show these scars of the knees. They are porcelain-white, irregularly zig-zag, and distributed over the lower end of the femur and over the outer, inner, and extensor surfaces of the knee. They were at first pinkish; never painful.

DISCUSSION.

DR. JACOBI: The case exhibits an excess of what we see in abnormal growths of the long bones. We all notice after cases of typhoid fever or scarlatina that the child grows very rapidly. It is the result of epiphyseal and periepiphyseal hyperemia, not followed by abnormal ossification. It is not the lying in bed that has anything to do with it, but it is an exaggeration of the normal processes. The reverse is seen in rachitis. In that disease we have inflammation of the epiphyses, which is followed by rapid ossification. By this ossification the growth is stunted. That is why in rickety children we have short limbs, while those who have infectious fevers are apt to grow quite rapidly.

DR. OSLER: The condition is not always due to the rapid growth, but it may be due to exactly the reverse, rapid atrophy in the fevers. It is not very uncommon after typhoid. I have a friend who had these scars appear on his back, producing a most remarkable appearance, following typhoid fever when he was at least thirty. There are splits in the corium in which you can almost lay your finger. I have reported cases after scarlet fever and following a great increase in girth due to fat.

DR. JANEWAY: It is not only in the pregnant woman that you find these markings on the abdomen, as might be inferred from what has been said. We frequently find them in very fat men. I have seen a number of men with this appearance so marked that had it been in a woman it would have suggested pregnancy.

TWO CASES OF GENERAL GONOCOCCAL PERITONITIS IN YOUNG GIRLS UNDER PUBERTY, ONE SIMULATING APPENDICITIS: OPERATED.

By W. P. NORTHRUP, M.D.,
OF NEW YORK CITY.

THESE two cases are presented with the hope that they may teach someone else as much as they have taught the writer.

Two girls, sisters, aged nine and eleven years, acquired vulvovaginitis, developing one week later into peritonitis. The source of infection was a female in the household with whom each occasionally shared a bed. The girls slept together, and it may be that Case II. contracted it from Case I., or that both acquired it from the same source. Their symptoms had the same sequence, those of Case II. developing regularly one week behind Case I. Case I. showed symptoms referable to the appendix, and was operated for appendicitis; Case II. was not. Both fully recovered.

CASE I. *Gonococcal vulvovaginitis; peritonitis; suspected appendicitis; laparotomy; recovery; girl eleven years old.*—The patient was put to bed for a few days because she was not feeling quite as well as usual. It was then discovered that she had a vaginal discharge. On account of these signs and symptoms a physician was summoned. She seemed to be doing fairly well under general treatment with cleansing washes. The condition was such that the physician did not think it necessary to see her the day before, nor did he expect to on the day now to be recorded. She had been ailing one week.

The following is the story of the seventh day: At 11 o'clock, the patient being as well as on previous days, was placed in an arm chair on the balcony, to get the air and to be entertained. It was noted while she was sitting there that she seemed to be getting tired; she was put to bed. At 1 o'clock the temperature was 103° F. She felt, as it was reported, "sick." She had abdominal pain, vomited once, had fever and great prostration. The pain was greatest in the right iliac fossa, where she was very sensitive to pressure. The most casual observer would be struck by her appearance—

the death-like pallor and the profound prostration. She was apparently in shock. This latter symptom reminded me of the relaxation, profound prostration, and pallor which I have seen in two infants with intussusception. To very few conditions would Dr. Delafield's favorite and impressive expression apply with more force: "she looks sick."

By 3 o'clock the temperature was 104° F. By 4 o'clock the temperature was 104½° F.

To recapitulate, the symptoms were: abrupt onset, pain in abdomen, tenderness most marked in right iliac fossa, moderate abdominal distention, vomiting (once), painful micturition, ghastly pallor, marked prostration, extreme relaxation, temperature, 104½°. It may be remarked that all these adjectives are deservedly strong.

The vulvovaginal discharge was thick, creamy, containing intracellular diplococci, decolorizing by Gram's stain, and pronounced gonococci by Dr. G. A. Tuttle. Dr. George Woolsey, surgeon, was called in consultation. He confirmed the findings above. He noted, further, rigidity over the appendix, the size of the palm of one's hand, with acute pain on pressure. No mass was made out. Right rectus muscle was rigid; breathing thoracic. Temperature then was 104½ F. In his opinion there was beginning general peritonitis, due probably to a lesion of the appendix. Dr. Woolsey performed laparotomy six hours from the time the patient was sitting on the balcony and just beginning to be "drooping" and sick.

The following is a memorandum of the operation and a privileged *intra vitam* examination of the pathological lesions:

The operation was intermuscular. Small opening; wound closed. Few drachms of straw-colored, clear fluid found deep in the pelvis. The peritoneum was red; the vessels distended in a manner to cause remark by each observer in turn. It was a most striking example of "arborescent injection." The peritoneum seemed just as red as injected vessels could possibly make it; especially was this marked over the cecum. Beyond this extreme injection of vessels and the few drachms of fluid in the pelvic fossa there was no obvious inflammatory change. It was afterward commented upon that the membrane was less glistening than usual, a little duller and "sand-papered," though not dry. The appendix was healthy; the tubes and ovaries were not removed. Though the injection of vessels was noted in all the coils of intestines exposed to view, the injection was most marked on the cecum and colon. These last were blood-red.

This condition of the peritoneum would correspond to the description of cellular peritonitis given by Delafield and Prudden, sixth edition, page 521. It is, in abstract, as follows: Incited by an irritant acting not too long and not too energetically, the entire peritoneum may be congested, but there are no exudates and no other obvious lesion. Minute examination, however, shows a very marked change in the mesothelial (endothelial) cells; they are increased in size and number. The new cells coat the surface of the peritoneum and project outward in little masses.

The patient recovered without incident; vulvovaginal discharge continued three months (Case II. two months). After more than a year has elapsed the nurse who was in attendance reports the patient entirely well.

Case II. *Gonococcal vulvovaginitis; general peritonitis, not simulating appendicitis, not operated; recovery; girl nine years old.*—This patient, a sister of the first, had been sleeping with Case I. and with the female by whom Case I. was probably infected. Cases I. and II. ran much the same course. Vulvovaginal discharge was noted one week after the beginning of discharge and about the time of beginning of pain in Case I. She was kept in bed and treated by selected diet, attention to bowels and frequent washings with boric acid solution. The discharge was thick, creamy, containing gonococci, decolorizing by Gram's stain (Dr. George A. Tuttle). At the end of one week she was seized with pain in abdomen, vomiting, painful and frequent micturition; tenderness and pain, referred always to region of spleen. Pain and sensitiveness and resistance were over whole abdomen, but when asked to point to place of greatest tenderness and pain, she invariably put her finger over left upper portion of abdomen. She vomited large quantities, and for many days. Distention slight. Pain was colicky, shifting its location. Everything which increased peristalsis created rumbling and brought on colicky pains. The patient lay much of the time with her knees drawn up, dreading the moment when she must empty her bladder or bowels, putting it off just as long as possible. She would sometimes cry piteously for thirty minutes before she could be induced to use the bed-pan. Respiration was rapid and thoracic, sleeping and waking. The chest was examined repeatedly, to exclude pneumonia and bronchitis. None was discovered. The general appearance of this nine-year-old child was characteristic. In the first place she was a pure blonde. In the description by the French writers is mentioned a ghastly pallor with algidity. Our nine-year-old blonde was pale, blue, pinched; her nose, hands, and feet cold; her nose and lips thin and pinched; her forehead wrinkled, scowling; her face having an anxious or agonized expression, as though about to cry. She lay on her side, knees drawn well up, moaning and whimpering. The sympathetic nurse each day spoke of her growing thinner, "pinched," spoke of her ghastly pallor, and added, "She looks positively blue at times." The notes speak daily of pains for seventeen days, and occasionally for a longer period. Temperature irregular, reaching on one occasion 102.2° F. For more than one week it varied between 101° and 102°, and for a second week between 101° and 102°, and for a third week between 99° and 100°. Vulvovaginal discharge two months. After more than a year the nurse reports the case entirely well.

These two cases are called here general gonococcal peritonitis. The gonococcus in the discharge was fully established by competent authorities, the two cases showing the same, likewise the case from which the two contracted it. The general peritonitis of Case I. was established

not only by characteristic outward signs and symptoms, but by operation, which allowed of thorough inspection of most of the peritoneal surfaces. But one proof remains unpresented: we, in our anxiety to have the operation completed during daylight, forgot to take cultures of fluid found in the peritoneum.

As to the connection between the vulvovaginitis and the peritonitis, the presumption amounts to conviction that the infecting agent was propagated thither by way of the uterus and tubes. The tubes were slightly inflamed, but their condition did not call for their removal.

In Case II. the diagnosis was based on the experience gained in Case I. The two cases were different in but one point—that the pain and greatest tenderness of Case II. were referred to the splenic region. After seeing the peritoneal lesion of Case I. there was no thought of operation. On the same basis, and on comparing these cases with those reported in literature, the prognosis was considered good.

In nearly all recorded cases the sudden onset of peritonitis took up the attention of the physicians, and the vulvovaginal discharge was discovered afterward. Frequently the discharge became scanty the moment peritonitis began, and the discharge was discovered quite by chance.

Our cases were in bed from the first on regulated diet, and were skilfully nursed. This did not save them from extension of inflammation.

Abrupt onset characterized both cases. Pain and tenderness, prostration and pallor were most pronounced. There were noted also pinched features, anxious expression, algidity, rapid thoracic respiration, painful micturition and defecation. From all recorded French cases and from the two above, one gains the impression that there is something characteristic about the picture of ghastly pallor and algidity, profound prostration and relaxation, which suddenly lays low these young girl patients. They present a picture not easily forgotten: pinched and blue; pale and relaxed; whimpering and flexed.

Dr. Jules Comby,[1] in his study of eight cases, most comprehensively says: "The onset of gonococcal peritonitis is absolutely unforeseen and brutal." Again: "Do not be surprised to see ending rapidly and favorably cases of peritonitis (gonococcal) which have begun in an explosive manner."

[1] Archives de Médecine des Enfants, vol. iv., No. 9, p. 513, Paris, September, 1901.

DISCUSSION.

Dr. Kinnicutt: A sufficient number of these cases have now been published to demonstrate that the prognosis is decidedly favorable without operation. The peritoneum is not a favorable soil for growth of the gonococci. Although the onset may be severe, the effects of the infection are short-lived and the cases apparenty tend to get well without surgical interference.

Dr. Jacobi: These cases are not so very infrequent. Every one of us has seen a good many of such cases more or less severe in character. As Dr. Kinnicutt has said, the prognosis is good if one has the patience to wait. I have seen adhesions as a result when operations have been done for other causes years after such cases ran their full courses. Peritonitis cannot heal, probably, without these adhesions forming. I consider it a rather frequent disease. Where little girls are together in a ward, if there is one case among them there may be a half-dozen in a short time.

Dr. Northrup: What is the prognosis as to the development of the genital organs of girls afflicted with this trouble before puberty?

Dr. Jacobi: From what I have seen I believe there is a good opportunity for the development of chronic salpingitis, which, however, need not always be purulent.

THE RELATION OF CHRONIC ENLARGEMENT OF THE SPLEEN TO ANEMIA IN INFANCY.

By JOHN LOVETT MORSE, M.D.,
OF BOSTON.

The objects of this paper are to consider the relation of chronic enlargement of the spleen and anemia in infancy to each other, and whether or no there is any justification for the recognition of the special forms of anemia known as the "splenic anemia of infancy" and "anemia infantum pseudoleukemica." Before taking up these subjects it may be well to consider briefly the peculiarities of the blood in infancy, both in health and disease, and the conditions under which chronic enlargement of the spleen occurs at this age.

The blood of infants under two years normally differs in certain of its characteristics from that of adults. The hemoglobin, although relatively high for a short time after birth, is, during the rest of childhood, relatively low. The number of red corpuscles is about the same or a little larger than in adults, averaging a little over five millions per cubic millimeter. During the first weeks of life there is more or less variation in the size and shape of the red cells, and nucleated forms are not very unusual. The number of white corpuscles per cubic millimeter is somewhat larger than in adults, averaging from ten thousand to fourteen thousand. The relative proportions of the various forms of leukocytes are also considerably different. The limits are roughly as follows: Small mononuclear, 50 per cent. to 70 per cent.; large mononuclear, 5 per cent. to 15 per cent.; polynuclear neutrophiles, 30 per cent. to 40 per cent.; eosinophiles, 1 per cent. to 10 per cent.; that is, the proportion of mononuclear forms is about three times as great as in adult life, while that of the polynuclear neutrophiles is only one-half as large. The mononuclear cells, moreover, are not merely lymphocytes, but vary much, not only in

the size of the cell as a whole, but also in the size of the nucleus and in the amount of protoplasm.

Blood changes develop more easily and more frequently as the result of various morbid conditions and diseases in infants than in adults. All the changes seen in the blood of adults as the results of disease are exaggerated in infancy. The tendency is always to revert to a younger or to the fetal type of blood. All forms of blood disease in infancy are apt to be associated with splenic enlargement. As the result of this tendency to exaggeration of changes and to reversion to a younger type of blood, the red corpuscles show much greater variety in size and shape and many more nucleated forms than under similar pathologic conditions in the adult. Leukocytosis also develops more rapidly and to a greater degree. Its type, moreover, is not constant, as in adults, in whom the increase of white cells is largely in the polynuclear neutrophiles. In infants the increase is sometimes in the lymphocytes, sometimes in the large mononuclear forms, sometimes in the polynuclear neutrophiles, and sometimes, even, in the eosinophiles. Leukocytosis is more apt to occur in blood conditions associated with splenic enlargement than in those without it. Myelocytes occur in less severe conditions and in greater numbers than in adults. An increase in the number of eosinophilic cells, even if considerable, seems to be of little significance. The percentage of hemoglobin is almost always relatively low.

Chronic splenic tumor is much more common in infancy than in later years, occurring not only under the same conditions as in adults, but in many others not associated in them with splenic enlargement. It is, as in adults, an almost constant accompaniment of leukemia, pseudoleukemia, cirrhosis of the liver, and malaria. These conditions, with the exception of malaria, are extremely rare in infancy. Malaria however, is not at all uncommon. In it the splenic tumor develops early, attains considerable size and persists a long time. Enlargement of the spleen from amyloid change occurs in association with amyloid changes in other organs as in adults and from the same causes. Malignant disease of the spleen is almost unknown in infancy, but does occur. If so, it is usually congenital or secondary to malignant disease elsewhere. Primary endothelial hyperplasia of the spleen (Bovaird) has not yet been seen under two years.

In adults chronic diseases are not, as a rule, associated with enlarge-

ment of the spleen. Many of the chronic affections of infancy, however, especially those in which cachexia is marked, are accompanied by enlargement of the spleen. It is in this class that the enlargements of the spleen in syphilis and rachitis probably belong. It is almost invariably enlarged in the hereditary syphilis of infancy. This enlargement is usually due to an increase in the stroma and to thickening of the bloodvessels, but may in rare instances be due to gummatous changes. Enlargement of the spleen occurs very commonly in rickets. Its direct dependence on the disease *per se* is, however, doubtful. In tuberculosis the enlargement, unless due to amyloid changes, is usually slight. It is especially common in conditions associated with anemia, all forms of which, whether primary or secondary, may be associated in infancy with enlargement of the spleen.

Before going further it may be well to attempt to define what is meant by the terms "splenic anemia of infancy" and "anemia infantum pseudoleukemica." Certain authors, usually English, have apparently considered chronic enlargement of the spleen *per se* as sufficient to justify the use of the term "splenic anemia." Most of the others have, however, evidently used the term to describe the clinical complex more commonly known as "anemia infantum pseudoleukemica." There can be but little doubt that the terms "splenic anemia of infants," "anemia splenica infantile," "anemia splenica infettiva dei bambini" and "anemia infantum pseudoleukemica" have been applied to practically identical conditions and may be considered as synonymous. No two authors are agreed as to just what are the pathognomonic symptoms, physical signs, and blood condition of anemia infantum pseudoleukemica. A combination of the descriptions of von Jaksch, Luzet and Alt and Weiss describes it as well, perhaps, as anything. (Dr. A. H. Wentworth[1] has recently reviewed the literature of this condition very thoroughly.)

It is a form of severe progressive anemia of infants whose symptoms and clinical course correspond to the picture of leukemia. There is marked enlargement of the spleen and more or less enlargement of the liver. The superficial lymph nodes are usually enlarged. The course is less rapid and the prognosis better than in leukemia. The blood condition is as follows: Constant diminution in the number of

[1] Boston Medical and Surgical Journal, 1901, cxlv., 374, 402, 435, 461, 488.

red corpuscles with a more or less marked diminution in the amount of hemoglobin; poikilocytosis; very many nucleated red cells, chiefly normoblasts, many of these of abnormal form and showing karyokinetic figures; more or less polychromatophilia of the nucleated red cells and many of the non-nucleated; generally marked leukocytosis, always polymorphous.

Pathologic examinations have been few in these cases, and, as a rule, very incomplete. The lesions which have been described in the spleen are almost entirely those of chronic hyperplasia, affecting various parts of the organ in different degrees in individual cases. The livers showed congestion and slight increase in the connective tissue. In some cases there was a slight infiltration of lymphoid cells and in others slight degenerative lesions.

I have notes, with complete examinations of the blood, on twenty-two cases of chronic enlargement of the spleen in infancy, as well as notes without examinations of the blood on a number of others. For lack of a better basis, I have arranged them primarily according to the size of the spleen, and secondarily according to the size of the liver.

Case I.—Joseph C., aged eleven months, was admitted to the Infants' Hospital January 3, 1901. He had had the breast alone for six months, after that a varied diet. He had always vomited a great deal. The history was otherwise imperfect.

He was well developed, fairly nourished, and flabby. The skin was in good condition. There was marked pallor of the skin and mucous membranes. The fontanelle was level. There were two lower incisors. There was a moderate rosary. The cardiac impulse was in the fifth space 1½ cm. outside the nipple line. The upper border of cardiac dulness was at the lower border of the second rib, the right border 3 cm. to the right of the median line, the left 7½ cm. to the left of the median line. The first sound over the whole precordia was continued into a soft, blowing murmur. The second pulmonic sound was the louder. The lungs were negative. The spine showed a marked curve of weakness. The upper border of liver flatness was in the fifth space. The lower border was palpable 4 cm. below the costal border in the nipple line. The spleen was palpable 1 cm. below the costal border. There was a slight umbilical hernia. There was a slight enlargement of the epiphyses at the wrists. The extremities were otherwise normal except for slight edema of the feet and legs. There was no edema of the hands, but a little of the eyelids.

Urine. Pale, clear, acid, 1017, no albumin.

Blood. Extremely watery and streaky, coagulation very slow; hemo-

globin, 15 per cent.; red corpuscles, 1,250,000; white corpuscles, 10,300; small mononuclear, 67 per cent.; large, mononuclear, 2 per cent.; polynuclear neutrophiles, 29 per cent.; eosinophiles 2 per cent. There was marked variation in the size and shape of the red corpuscles. There was a tendency to small forms rather than to large. No nucleated forms were seen in two slides.

In spite of careful feeding, iron and arsenic, he failed steadily in weight, strength, and color. The temperature was slightly elevated. There was almost no vomiting. The movements were clay-colored. The edema of the face increased.

He died February 3, 1901.

CASE II.—William F., aged ten months, came to the Out-patient Department of the Infants' Hospital May 17, 1898. There was no history of tuberculosis in the family or of exposure to it. He had nothing but breast milk, but was fed irregularly. A rough analysis of the breast milk showed a specific gravity of 1031 and 2.6 per cent. fat. The proteids must, therefore, have been about normal or a little low. He began to lose weight, strength and color at seven months, and had failed steadily since then. He had had no fever. The bowels moved once daily. He vomited a little almost every day.

He was poorly developed and nourished. Pallor was marked. The head was negative. There were two teeth. He held up his head, but was unable to sit alone. There was a moderate rosary. The heart and lungs were normal. By auscultatory percussion the stomach was distended. The liver was normal. The spleen was palpable 2 cm. below the costal border. The extremities were normal. There was a slight general enlargement of the lymph nodes.

Blood. Hemoglobin, 42 per cent.; red corpuscles, 3,288,000; white corpuscles, 4800; small mononuclear, 49 per cent.; large mononuclear, 5 per cent.; polynuclear neutrophiles, 45 per cent.; eosinophiles, 1 per cent. There was moderate variation in the size and shape of the red corpuscles. One macroblast and one normoblast were seen in counting 100 white cells.

When last seen, June 22, 1898, the symptoms had continued, and he had failed steadily in every way. He presumably died shortly after.

CASE III.—Joseph E., aged five months, came to the Out-patient Department of the Infants' Hospital May 9, 1898. He had never had any food but breast milk. He vomited after almost every nursing. The bowels were constipated. He had never gained.

He was small, but not much emaciated. The pallor was marked. The head was negative. He was unable to hold it up. There was a marked rosary. The heart was normal except for a systolic murmur over the whole precordia. A few râles were heard here and there in both chests. The abdomen was lax. The liver was normal. The spleen was palpable about 2 cm. below the costal border. The epiphyses at the wrists were slightly enlarged. The extremities were otherwise normal. There was a slight general enlargement of the lymph nodes.

Blood. Hemoglobin, 57 per cent.; red corpuscles, 4,519,000; white corpuscles, 15,000; small mononuclear, 44 per cent.; large mononuclear, 3.5 per cent.; polynuclear neutrophiles, 47 per cent.; eosinophiles, 5.5 per cent. There was but little variation in the size of the red corpuscles and very little in their shape. One normoblast was seen in counting 400 whites.

He died November 25, 1898, "of the same trouble."

Case IV.—Joseph M. was admitted to the Infants' Hospital in May, 1900, when sixteen months old. He had been fed on condensed milk and malted milk, and had never done well. He had always had vomiting and diarrhea off and on, and had never gained.

He was small, thin and markedly pale. The fontanelle was small and much sunken. There were eleven teeth. The costal cartilages were much depressed, making the front of the chest flat. There was a moderate rosary. The heart and lungs were normal. There was a loud systolic blow in the neck. The abdomen was lax. The liver was normal. The spleen was palpable about 2 cm. below the costal border over a distance of 5 cm. The edge was sharp and the notch distinctly felt. The extremities were normal. There was a moderate general enlargement of the lymph nodes, especially of those in the right side of the neck.

Blood. Hemoglobin, 25 per cent.; red corpuscles, 2,296,000; white corpuscles, 16,850; small mononuclear, 34.4 per cent.; large mononuclear, 19.6 per cent.; polynuclear neutrophiles, 44.4 per cent.; eosinophiles, 0.4 per cent.; myelocytes, 1.2 per cent. The red corpuscles were somewhat irregular in size, shape, and color, but poikilocytosis was not marked. In counting 250 white corpuscles, 6 normoblasts, 1 microblast and 1 megaloblast were seen. After a few weeks of observation he was discharged to die.

He was seen September 8, 1902, two and one-half years later. He was then well and strong and of good color. The liver was normal. The spleen was not palpable.

Case V.—Francis K., aged sixteen months, was admitted to the Infants' Hospital January 12, 1901. He was well until he was weaned at fourteen months and put on general diet. After that he was constipated, vomited occasionally, and lost weight pretty steadily. When weaned he could stand and walk with the aid of a chair. At entrance he was unable to stand.

He was well developed and nourished, but slightly flabby and rather pale. The fontanelle was 3 cm. in diameter. The head was not otherwise abnormal. There were twelve teeth. The spine showed a slight curve of weakness. There was a slight rosary and slight flaring of the lower chest. The heart showed nothing abnormal excepting a faint systolic murmur in the pulmonic area. There was a venous hum in the neck. The lungs were normal. The upper border of the liver flatness was at the fifth rib. The lower border was palpable 3 cm. below the costal border. The spleen was palpable 2 cm. below the costal border and was 4 cm. in width. The abdomen was negative. There was slight enlargement of the epiphyses at the wrists.

Urine. Normal color, alkaline, no albumin.

Blood. Hemoglobin, 65 per cent.; red corpuscles, 5,072,000; white cor-

puscles, 16,600; small mononuclear, 40 per cent.; large mononuclear, 18 per cent.; polynuclear neutrophiles, 41 per cent.; eosinophiles, 1 per cent. There was moderate variation in the size of the red corpuscles, but little in their shape. No nucleated forms were seen. No abnormal forms of white cells were seen, but there was great variation in the size of the mononuclear cells, very few of them being small.

He was discharged January 19, 1901, improving in every way. He did not vomit, his movements were normal, and he was gaining in weight. Nothing further is known as to the progress of the case.

Case VI.—Alice F., aged five months, came to the Out-patient Department of the Infants' Hospital June 22, 1897. She had always been fed on sterilized milk or condensed milk. She had always vomited and had undigested movements. She had gained fairly steadily in weight.

She was fairly developed and nourished, and very pale. The heart was normal except for a systolic murmur over the whole precordia. The lungs were normal. The liver was normal. The spleen was palpable 3 cm. below the costal border and was 4 cm. wide. There was a slight umbilical hernia. There was a general enlargement of the lymph nodes more marked in those of the groin.

Blood. Hemoglobin, 25 per cent.; red corpuscles, 1,736,000; white corpuscles, 4200; small mononuclear, 69 per cent.; large mononuclear, 5 per cent.; polynuclear neutrophiles, 25 per cent.; eosinophiles, 1 per cent. There was marked variation in the size and moderate variation in the shape of the red corpuscles. No nucleated forms were seen.

Nothing further is known as to the progress of the case, except that she died July 20, 1897.

Case VII.—Helen G., aged ten months, came to the Out-patient Department of the Infants' Hospital July 2, 1897. She was about a month premature. She was nursed for five months, and then given condensed milk with cereals. She had never been strong, and had always been constipated. She was brought because of fever, crying, and sleeplessness for a month.

She was well developed and nourished, but of a very pale, lemon-yellow color. She had no teeth. There was a slight rosary. There was a slight systolic murmur over the whole precordia. The lungs were normal. The liver was not enlarged. The spleen was palpable 3 cm. below the costal border and was 6 cm. wide. There was a slight general enlargement of the lymph nodes.

Blood. Hemoglobin, 30 per cent.; red corpuscles, 3,708,000; white corpuscles, 18,520; small mononuclear, 31 per cent.; large mononuclear, 4 per cent.; polynuclear neutrophiles, 64 per cent.; eosinophiles, 1 per cent. There was marked variation in the size and shape of the red corpuscles, many of them being very large. Five normoblasts were seen in counting 500 whites.

She was last seen July 29, 1897, and at that time was doing well in every way.

Case VIII.—Joseph D., aged twenty-one months, was admitted to the Infants' Hospital June 9, 1902. No history came with him.

He was well developed and nourished, but flabby. The anterior fontanelle was 2 cm. in diameter. The frontal and parietal eminences were somewhat enlarged. There were twelve teeth. There was a marked rosary and a slight retraction of the ribs at the insertion of the diaphragm. The heart and lungs were normal. The level of the abdomen was much above that of the thorax. The liver was palpable 3 cm. below the costal border. The spleen was palpable 3 cm. below the costal border and was 4 cm. wide. The surface was smooth, the edge sharp, the notch palpable. The extremities were normal except for considerable enlargement of the epiphyses at the wrists. There was a slight general enlargement of the lymph nodes.

Blood. Hemoglobin, 65 per cent.; red corpuscles, 5,380,000; white corpuscles, 15,625; small mononuclear, 43 per cent.; large mononuclear, 2 per cent.; polynuclear neutrophiles, 54 per cent.; eosinophiles, 0.5 per cent.; myelocytes, 0.5 per cent. There was slight variation in the size and shape of the red corpuscles. No nucleated forms were seen.

He was lost sight of, and nothing is known as to the further history.

Case IX.—Sylvia V., aged eleven and one-half months, entered the Infants' Hospital May 27, 1899. Nothing was known as to her history except that she had had whooping-cough in February. There was not much cough at that time, but the appetite was poor, she vomited occasionally and had a sore mouth.

She was markedly emaciated and very pale. There was a systolic murmur over the whole precordia. There was an occasional râle in both chests. The liver was normal. The spleen was palpable about $3\frac{1}{2}$ cm. below the costal border. There was slight general enlargement of the superficial lymph nodes. The body and extremities were covered with a fine purpuric eruption. The eyelids were puffy. There were a few hemorrhagic spots in the mouth. There was no edema of the extremities.

Blood. Markedly pale and yellow. Hemoglobin, 19 per cent.; red corpuscles, 950,000; white corpuscles, 27,000; small mononuclear, 52 per cent.; large mononuclear, 13 per cent.; polynuclear neutrophiles, 32 per cent.; eosinophiles, 0.5 per cent.; myelocytes, 2.5 per cent. There was marked variation in the size and moderate variation in the shape of the red corpuscles. In counting 500 white cells, 22 megaloblasts, 8 microblasts, 24 normoblasts and 12 atypical nucleated red cells were seen.

She took but little food and vomited a great deal. The movements were fairly normal. The temperature rose steadily, and she died June 1, 1899.

Case X.—Sadie C., aged twenty months, came to the Out-patient Department of the Infants' Hospital June 20, 1896. She was fed at first on the breast, but was soon given patent foods and then put on a general diet. She had always had more or less trouble with her digestion. She could sit and stand alone, but was unable to walk.

She was fairly developed and nourished, but flabby and pale. She had a large, square, flat head. The fontanelle was nearly closed. There were eleven teeth. There was a marked curve of weakness. There was a very marked rosary, pigeon breast, and marked retraction of the ribs at the inser-

tion of the diaphragm. The heart and lungs were normal. The liver was not enlarged. The spleen was palpable about 4 cm. below the costal border and was 8 cm. wide. The abdomen was large and soft. There was marked enlargement of the epiphyses at the wrists and moderate bow-legs. There was a slight general enlargement of the lymph nodes.

Blood. Hemoglobin, 68 per cent.; red corpuscles, 5,158,000; white corpuscles, 15,200; small mononuclear, 51 per cent.; large mononuclear, 5 per cent.; polynuclear neutrophiles, 40 per cent.; eosinophiles, 4 per cent. There was considerable variation in the size and shape of the red corpuscles. Macrocytes were numerous. An occasional normoblast was seen.

She was seen October 7, 1902, when a little more than seven years old. She was then perfectly well. The tip of the spleen was just palpable.

CASE XI.—Minnie B., aged eighteen months, was admitted to the Infants' Hospital January 1, 1902. No history came with her.

She was fairly developed and nourished, but flabby and rather pale. The fontanelle was nearly closed. The parietal eminences were enlarged. There were twelve teeth. There was a slight rosary and flaring of the lower ribs. The heart and lungs were normal. The upper border of the liver flatness was at the fifth rib, the lower border was palpable 6 cm. below the costal border. The spleen was palpable 4 cm. below the costal border. The surface was smooth, the consistency firm, the edge rounded and the notch distinct. The epiphyses at the wrists and ankles were enlarged and there was slight bow-legs. There was a slight general enlargement of the lymph nodes.

Urine. Normal, acid, 1012, no albumin.

Blood. Hemoglobin, 75 per cent.; red corpuscles, 5,650,000; white corpuscles, 11,800; small mononuclear, 32 per cent.; large mononuclear, 8 per cent.; polynuclear neutrophiles, 51 per cent.; eosinophiles, 9 per cent. There was very slight variation in the size of the red corpuscles and none in their shape or staining reaction. No nucleated cells were seen.

She was seen August 7, 1902. She was then perfectly well. The liver was palpable 4½ cm. below the costal border in the nipple line. The spleen was not palpable.

CASE XII.—Catherine A., aged twelve months, was admitted to the Infants' Hospital April 23, 1902. She had been fed on patent foods after the first two months. Her appetite had been poor. She had always vomited and had bad movements.

She was fairly developed and nourished, but pale. The frontal eminences were a good deal enlarged. The anterior fontanelle was 2 cm. in diameter and somewhat depressed. There was no craniotabes. There were two teeth. There was a purulent discharge from the left ear. There was a moderate rosary. The heart was normal. There was an occasional moist râle in both backs. The level of the abdomen was above that of the thorax. The liver was palpable 2 cm. below the costal border. The spleen was palpable, running out from beneath the costal border just inside the left nipple line, downward to the level of the umbilicus and then backward into the flank. The surface was smooth and hard and the edge sharp. The notch was not made

out. There was slight enlargement of the epiphyses at the wrists. There was a slight general enlargement of the lymph nodes.

Urine. Pale, no albumin.

Blood. Hemoglobin, 60 per cent.; red corpuscles, 3,564,000; white corpuscles, 16,250; small mononuclear, 31 per cent.; large mononuclear, 8 per cent.; polynuclear neutrophiles, 60 per cent.; eosinophiles, 1 per cent. There was marked variation in the size, shape and staining reaction of the red corpuscles. One megaloblast was seen while counting 100 whites.

She remained in the hospital about two weeks. While there she had very little fever and the lungs cleared up. The movements became normal and vomiting ceased.

She was seen December 19, 1902, eight months later. Her general condition was much improved. She was scarcely able to sit up alone. The liver was normal. The spleen was not palpable.

Case XIII.—Sam S., aged eight months, was admitted to the Infants' Hospital, May 11, 1902. He had always been breast-fed, but for the last three months had had more or less vomiting and been constipated.

He was fairly developed and nourished. Pallor was moderate. The fontanelle was level and 2 cm. in diameter. There were no teeth. There was a marked rosary and slight flaring of the lower chest. The heart and lungs were normal. The upper border of liver flatness was in the sixth space. The lower border was palpable 3 cm. below the costal border in the nipple line. The spleen was palpable, running out from beneath the costal border in the anterior axillary line, downward to the level of the umbilicus and upward into the flank behind the posterior axillary line. The surface was smooth, the edge sharp, the notch palpable. The abdomen was much enlarged, but lax. There was marked enlargement of the epiphyses at the wrists. There was a slight general enlargement of the lymph nodes.

Urine. High, acid, trace of albumin. Sediment: many pus cells and rarely a hyaline and granular cast.

Blood. Hemoglobin, not tested; red corpuscles, 5,800,000; white corpuscles, 15,000; small mononuclear, 43 per cent.; large mononuclear, 2 per cent.; polynuclear neutrophiles, 55 per cent. Typical signs of meningitis developed a little later, and the child died after an illness of a few days.

Case XIV.—Helen P., aged seven months, was admitted to the Infants' Hospital in January, 1902. Although she was breast-fed up to two weeks before entrance she had never done well after the first month. She had always vomited, had usually been constipated, but sometimes had had diarrhea. For the last two weeks she had been fed on Eskay's food.

She was small and poorly nourished. The skin was desquamating. There was a marked yellowish pallor. The fontanelle was level. There was a venous hum in the neck. There was a very slight rosary. The heart area was normal. The first sound over the whole precordia was continued into a blowing murmur, loudest and longest at the pulmonic area. The lungs were normal. The upper border of liver flatness was at the fifth rib. The lower border was palpable 3 cm. below the costal border. The spleen

was palpable, running out from behind the costal border about midway between the anterior axillary line and the nipple line, forward and downward to the level of the umbilicus in the nipple line, and backward into the flank. The surface was smooth and hard, the edge sharp, the notch palpable. The abdomen was negative. There was a considerable general enlargement of the lymph nodes. There were a few purpuric spots on the head, face, and legs, and a fine purpuric rash on the arms.

Urine. Straw-colored, slightly acid, no albumin.

Blood. Hemoglobin, 55 per cent.; red corpuscles, 2,553,000; white corpuscles, 8200; small mononuclear, 44 per cent.; large mononuclear, 4 per cent.; polynuclear neutrophiles, 50 per cent.; eosinophiles, 1 per cent.; myelocytes, 1 per cent. There was moderate variation in the size and shape of the red corpuscles, with a tendency to large, but not to oval forms. There was moderate variation in the staining characteristics of the red corpuscles.

She remained in the hospital about two weeks. She took her food poorly and vomited a good deal. The movements, however, were fairly normal. She lost weight steadily. At the time of discharge the blood showed: Hemoglobin, 70 per cent.; red corpuscles, 3,260,000; white corpuscles, 13,125. She was heard from in August, 1902. She was then "perfectly well."

CASE XV.—Alice C., aged ten months, was brought to the Out-patient Department of the Infants' Hospital July 14, 1897. She had always been fed on various "infant foods." She had never thrived, and had gained little or no weight. During the last few weeks she had lost both weight and strength. She had always vomited a good deal. She had had diarrhea for the first few months, but since then had been constipated, the movements being normal in color. Bunches were noticed in the neck and groins at five months; they had not increased markedly since. Depressed fontanelle, dryness of the skin and nocturnal fever had been present for three months. A tumor was first noticed a week before she came to the hospital. It had increased somewhat in size during this time.

She was poorly developed and emaciated. The skin was dry and brownish. The frontal bones were considerably lower than the parietal. The fontanelle was depressed and small. The frontal eminences were large. There were no teeth. There was a slight rosary. The heart and lungs were normal. There was dulness under the upper part of the sternum, but none at the root of the lungs. The upper border of liver flatness was at the sixth rib. The lower border was palpable 5 cm. below the costal border. The edge of the liver was firm and sharp. The spleen was palpable, running out from under the ribs in the left nipple line downward to the umbilicus and then backward into the flank just above the anterior superior spine. The surface was smooth, the consistency firm, the notch palpable. There was marked enlargement of all the superficial lymph nodes.

Blood. Hemoglobin, 60 per cent.; red corpuscles, 4,340,000; white corpuscles, 31,500; small mononuclear, 29.5 per cent.; large mononuclear, 9.9 per cent.; polynuclear neutrophiles, 56.5 per cent.; eosinophiles, 0.3 per cent.; myelocytes, 3.8 per cent. There was very marked variation in the size and

shape of the red corpuscles. Nucleated forms were very numerous. Of 100 nucleated cells 89 were macroblasts and 11 normoblasts. Six macroblasts showed nuclear figures. Many of the nucleated and some of the non-nucleated forms were polychromatophilic.

She was again seen August 9. At that time the spleen had diminished considerably in size. She died September 18. The mother wrote that she had had a hemorrhage from the bowels for two weeks before death, and that "the bunch in the side could not be felt."

Case XVI.—Charles G., aged ten months, came to the Out-patient Department of the Infants' Hospital July 11, 1898. He had been fed on the breast and condensed milk at home and had had cow's milk at a nursery. He had always had more or less diarrhea and vomiting, varying in severity from time to time. At times he seemed sick, at others not. He was always backward, and his head perspired profusely at night. There had been a gradual increase in the size of the abdomen for two months.

He was fairly developed but poorly nourished. His color was fair, the skin dry. The anterior fontanelle was large. There was no craniotabes. There was a purulent discharge from the nose. He had two teeth. He could hold up his head, but was unable to sit alone. There was a marked rosary and flaring of the lower ribs. The heart and lungs were normal. The liver flatness began at the eighth rib in the scapular line; the lower border was palpable 5 cm. below the costal border. The spleen could be felt running out from under the ribs in the nipple line, directly downward to the level of the umbilicus, backward at a right angle into the flank and upward in the posterior axillary line. The edge was sharp and hard, the surface smooth. The abdomen was considerably enlarged and rather tense. The epiphyses at the wrists were considerably enlarged, but the extremities were otherwise normal. There was a slight general enlargement of the lymph nodes.

Blood. Hemoglobin, 58 per cent.; red corpuscles, 4,408,000; white corpuscles, 47,220; small mononuclear, 36.5 per cent.; large mononuclear, 9.5 per cent.; polynuclear neutrophiles, 50.5 per cent.; eosinophiles, 1 per cent.; myelocytes, 2.5 per cent. There was moderate variation in the size and staining qualities of the red corpuscles, but very little in their shape. In counting 500 white corpuscles, 11 normoblasts, 1 microblast and 18 macroblasts were seen.

He was soon lost sight of, and nothing is known as to the further history of the case.

Case XVII.—Maude M., aged eight months, was admitted to the Infants' Hospital May 14, 1899. She undoubtedly had congenital syphilis. There was no further history.

She was small, pale, and poorly nourished. The head was somewhat flattened, the frontal and parietal eminences enlarged. The anterior fontanelle was 3 cm. in diameter and bulging. The superficial veins of the scalp were considerably enlarged. The nares were occluded, and there was considerable purulent discharge. The mouth was open, and the mouth and throat dry. There were no teeth. She held her head up feebly, but could

not sit alone. There was a very slight rosary. The heart and lungs were normal. The lower border of the liver was palpable 6 cm. below the costal border. The spleen could be felt coming out from behind the ribs in the anterior axillary line running downward to the level of the umbilicus and backward under the ribs at about the posterior axillary line. The surface was smooth, the edge sharp, the notch palpable. The abdomen was rather large. The extremities were normal except that the skin of the soles was dry and cracked. There was a general enlargement of the lymph nodes, including the postauricular and epitrochlear, to the size of beans.

Blood. Hemoglobin, 65 per cent.; red corpuscles, 4,200,000; white corpuscles, 13,400; small mononuclear, 42 per cent.; large mononuclear, 11 per cent.; polynuclear neutrophiles, 45 per cent.; eosinophiles, 2 per cent. There was moderate variation in the size of the red corpuscles, but little in their shape and staining reaction. No nucleated forms were seen.

She was discharged May 19, 1900. Nothing further is known as to the history of the case.

CASE XVIII.—Minnie L., aged seventeen months, was admitted to the Infants' Hospital November 13, 1895. She had never been nursed, but had been fed on condensed milk. She did not vomit. The bowels moved once in three or four days. The movements were large, hard, whitish, foul and contained a little mucus. A hard lump had been noted in the abdomen for two months. It was as large when first discovered as at admission. She had been pale for a long time, and had lost flesh rapidly in the last three months. She was just beginning to sit up alone.

She was fairly developed and emaciated. There was marked pallor, with a yellowish tinge. The fontanelle was not closed. She had four teeth, badly decayed. There was a moderate rosary. The heart and lungs were normal. The liver was normal. The spleen reached nearly to the median line, and extended to about 1 cm. above the anterior superior spine. The abdomen was full and tense. There was an umbilical hernia. There were a few purpuric spots on the abdomen. The epiphyses at the wrists and ankles were enlarged.

Urine. Normal.

Blood. Hemoglobin, 60 per cent.; red corpuscles, 3,556,000; white corpuscles, 12,400; small mononuclear, 28 per cent.; large mononuclear, 10 per cent.; polynuclear neutrophiles, 55 per cent.; eosinophiles. 7 per cent. There was marked variation in the size and shape of the red corpuscles. Macrocytes were more numerous than microcytes. There was a moderate number of nucleated red corpuscles, macroblasts being the most numerous. There was an occasional free nucleus. There were no abnormal forms of white cells.

She was heard from July 29, 1902, when about eight years old. She was said to be perfectly well in every way.

CASE XIX.—Jennie R., aged ten months, was admitted to the Infants Hospital June 1, 1901. She was breast-fed for five weeks, after that she was fed on a modified milk prepared at home. This mixture was a weak one and

was not changed for seven months. During this time she had no gastroenteric disturbances, but had gained weight very slowly. From this time until entrance, although still on a stronger modified milk, she had more or less disturbance of the bowels.

She was fairly developed and nourished. There was moderate pallor of the skin and mucous membranes. The anterior fontanelle was 3 cm. in diameter and level. The head was flattened on top and behind. There were two teeth. She sat alone, feebly. There was a moderate rosary. There was slight retraction of the chest at the insertion of the diaphragm. The heart and lungs were normal. The abdomen was distended. There was a slight umbilical hernia. The upper border of the liver flatness was at the upper border of the fifth rib; the lower border was palpable 3 cm. below the costal border. The spleen was felt running out from beneath the ribs in the anterior axillary line, downward just to the right of the umbilicus, then downward and backward to just above the anterior superior spine and backward into the flank. The surface was smooth; the consistency was firm; the notch was palpable in the nipple line. The spleen was apparently somewhat tender. The epiphyses at the wrists were enlarged. The extremities were otherwise normal. There was a slight general enlargement of the lymph nodes.

Urine. Pale, acid, 1010, no albumin or sugar.

Blood. Hemoglobin, 40 per cent.; red corpuscles, 4,000,000; white corpuscles, 18,750; small mononuclear, 34.4 per cent.; large mononuclear, 12.6 per cent.; polynuclear neutrophiles, 51 per cent.; eosinophiles, 0.2 per cent.; myelocytes, 1.8 per cent. The red corpuscles showed marked variation in size, shape, and staining reaction. There was no tendency to large forms, but a slight tendency to oval forms. Sixteen normoblasts and 9 megaloblasts were seen in counting 500 white corpuscles.

She was put on a stronger milk and beef juice, and was given maltine and oil and syrup of iron iodid. The temperature remained normal; she took her food fairly well and did not vomit. There was a tendency to constipation.

On June 16 the tip of the spleen only reached to 3 cm. to the left of the umbilicus. The examination of the blood on this date was as follows: Hemoglobin, 65 per cent.; red corpuscles, 5,132,000; white corpuscles, 18,580; small mononuclear, 23 per cent.; large mononuclear, 6 per cent.; polynuclear neutrophiles, 69 per cent.; eosinophiles, 1 per cent.; myelocytes, 1 per cent. There was moderate variation in the size and shape of the red corpuscles with slight variation in their staining reaction. There was a slight tendency to large and oval forms. In counting 500 whites, 1 microblast, 2 normoblasts and 10 megaloblasts were seen.

She had measles in the latter part of June. After that her improvement was even more rapid than before. The spleen was not palpable after August 1.

The examination of the blood August 16 was as follows: Hemoglobin, 65 per cent.; red corpuscles, 5,175,000; white corpuscles, 17,000; small mono-

nuclear, 48 per cent.; large mononuclear, 3 per cent.; polynuclear neutrophiles, 45 per cent.; eosinophiles, 4 per cent. There was slight variation in the size and very little in the shape of the red corpuscles. There was none in their staining reaction. No nucleated forms were seen.

She was seen November 29, 1902, eighteen months after her admission. She was then perfectly well in every way. The lower border of the liver was palpable 3 cm. below the costal border. The spleen was not palpable.

Case XX.—Gladys W., aged five months, was admitted to the Infants' Hospital April 29, 1902. The father undoubtedly had syphilis. There had been no miscarriages. The first child was well. This was the second child. She was normal at birth and was breast-fed. She developed snuffles at six weeks. She began to be pale at two months, and at the same time a fine rash appeared on the skin. Since she was three months old she had vomited a good deal, at times had had diarrhea, and had lost weight steadily.

She was small and poorly nourished. The anterior fontanelle was level. The posterior fontanelle was not quite closed. The superficial veins of the scalp were enlarged. Snuffles were marked. There was a slight rosary. The heart and lungs were normal. The liver was palpable 5 cm. below the costal border. The spleen was palpable, running out from behind the ribs in the anterior axillary line, forward to the left parasternal line at the level of the umbilicus, and downward and backward to the anterior superior spine, filling up the whole flank. The surface was smooth, the edge sharp, the notch indistinctly palpable at about the level of the umbilicus. The abdomen was large and tense. There was an umbilical and a right inguinal hernia. The palms and soles were desquamating. There was a moderate general enlargement of the lymph nodes.

Blood. Hemoglobin, 55 per cent.; red corpuscles, 3,750,000; white corpuscles, 16,200; small mononuclear, 50 per cent.; large mononuclear, 6 per cent.; polynuclear neutrophiles, 39 per cent.; eosinophiles, 5 per cent. There was very little variation in the size of the red corpuscles and none in their shape. There were no nucleated forms.

She improved rapidly on anti-syphilitic treatment, and was discharged May 12. Nothing is known as to the further history of her case.

Case XXI.—John C., aged seventeen months, was admitted to the Infants' Hospital April 21, 1902. He was the first child. He was fed on the breast for five months, and then was given strained rolled oats. He had vomited occasionally and had lost some weight. The history was very indefinite.

He was well developed and fairly nourished. His color was good. The fontanelle was closed. There was a slight rosary. The heart was normal. The lungs were normal. The lower border of the liver almost touched the anterior superior spine, reached to within 2 cm. of the umbilicus and passed under the left costal border in the left nipple line. The spleen was palpable, running out from beneath the costal border in the anterior axillary line directly downward to the level of the anterior superior spine and backward

into the flank. The surface was smooth, the density increased, the edge sharp, the notch not palpable. The abdomen was large and lax. The epiphyses were considerably enlarged at the wrists and moderated at the ankles. The legs were slightly bowed. There was a slight general enlargement of the lymph nodes.

Urine. Pale, 1008, no albumin.

Blood. Hemoglobin, 65 per cent.; red corpuscles, 3,720,000; white corpuscles, 10,700; small mononuclear, 30 per cent.; large mononuclear, 4 per cent.; polynuclear neutrophiles, 65 per cent.; eosinophiles, 1 per cent. There was a little variation in the size and none in the shape of the red corpuscles. No nucleated forms were seen.

He was seen November 29, 1902, seven months later. He was then a large fat, healthy looking baby. The liver was palpable 3 cm. below the costal border. The spleen was not palpable. His color was exceptionally good.

Case XXII.—Stanley A., negro, aged fourteen months, was admitted to the Infants' Hospital May 21, 1902. There had been no other children or miscarriages. He was breast-fed up to six months and was then put on Mellin's food. He had had no gastroenteric disturbances. He had had a cough off and on for two months.

He was small and poorly nourished. The head was much flattened on top and the forehead prominent. The anterior fontanelle was 3 cm. in diameter. The bridge of the nose was flattened. There was marked snuffles. There was marked pallor of the mucous membranes. There was a slight rosary, and the sides of the chest were somewhat flattened. The heart was normal. The lungs were normal except for an occasional moist râle. He sat up, but feebly. The liver was palpable 3 cm. below the costal border in the nipple line. The spleen was felt running out from beneath the ribs just outside the left nipple line downward and forward to 2 cm. below and about 1 cm. outside the navel, then back into the deep abdomen. The anterior border, tip and a portion of the lower and external borders were easily made out. It then disappeared into the deep abdomen. The anterior edge was rather sharp, the surface smooth, the notch distinct. It was not tender. The whole spleen was easily movable. The abdomen was generally enlarged, but lax. There was a slight enlargement of the epiphyses at the wrists. There were knock-knees. There was a moderate talipes valgus on both sides. There was a slight general enlargement of the lymph nodes. There were no rhagades and no fissures or mucous patches about the anus. There was pigmentation on the face and about the anus, as if there had been an eruption at some time. The soles were dry and desquamating.

Urine. High, acid, 1022, no albumin.

Blood. Hemoglobin, 50 per cent.; red corpuscles, 3,750,000; white corpuscles, 29,600; small mononuclear, 30 per cent.; large mononuclear, 18 per cent.; polynuclear neutrophiles, 48 per cent.; eosinophiles, 2 per cent.; myelocytes, 2 per cent. There was marked variation in the size and shape of the red corpuscles, but no tendency to oval or large forms. There was a

slight general polychromatophilia. In counting 200 white cells, 7 microblasts, 8 normoblasts, and 12 macroblasts were seen. There was marked polychromatophilia of the nucleated forms. The most striking thing in the blood was the great number of large mononuclear cells with large, feebly staining nuclei and a small amount of feebly staining protoplasm.

The temperature at entrance was 101° F. It began to rise the next day without any apparent cause. The physical examination was entirely negative. The temperature reached 107° on May 24, and the child died that night.

ILLUSTRATIVE CASES OF SECONDARY ANEMIA IN INFANCY.

CASE XXIII.—George T., aged eleven months, was admitted to the Infants' Hospital March 6, 1902. He was premature, at seven months. He had always been fed on undiluted cow's milk. He had always cried a great deal, vomited after feeding, and had always been constipated. He had never gained.

He was poorly developed and nourished. There was marked pallor of the skin and mucous membranes. There was a slight rosary. The heart and lungs were normal. The liver was normal. The spleen was not palpable. The abdomen was negative. There was a slight enlargement of the epiphyses at the wrists and ankles. There was a moderate general enlargement of the lymph nodes.

Urine. Normal, acid, no albumin.

Blood. Hemoglobin, 25 per cent.; red corpuscles, 2,600,000; white corpuscles, 15,000; small mononuclear, 63 per cent.; large mononuclear, 3 per cent.; polynuclear neutrophiles, 33 per cent.; eosinophiles, 1 per cent. There was marked variation in the size of the red corpuscles, but none in their shape or staining reaction. No nucleated forms were seen.

He was seen November 24, 1902, nearly eight months later. There has been no improvement in any way. The spleen was not palpable.

CASE XXIV.—Joseph B., aged twenty-two months, was seen July 22, 1897. His digestion had always been very feeble and he had always been pale. He had had bronchitis in the winter and more or less nasal discharge since then. For two weeks he had been running a moderate temperature, and the pallor had increased.

He was well developed and nourished, but very pale. There was a slight rosary and a slight general enlargement of the lymph nodes. The physical examination was otherwise negative.

Blood. Hemoglobin, 42 per cent.; red corpuscles, 4,560,000; white corpuscles, 29,720; small mononuclear, 45 5 per cent.; large mononuclear, 6 per cent.; polynuclear neutrophiles, 47.5 per cent.; eosinophiles, 1. There was much variation in the size and shape of the red corpuscles. No nucleated forms were seen.

He eventually entirely recovered.

CASES OF ANEMIA AND SPLENIC TUMOR WITHOUT EXAMINATION OF THE BLOOD, BUT WITH RECOVERY.

Case XXV.—William F., aged eighteen months, was seen in consultation with Dr. J. P. Torrey, of Andover, July 29, 1899. He had always been very pale, but had been well in other ways.

He was well developed and nourished. Pallor was marked. The anterior fontanelle was closed. He had sixteen teeth. There was a slight rosary. The heart was normal. The liver was normal. The spleen reached nearly to the umbilicus. The surface was hard, the edge thin, the notch palpable. The abdomen was negative. The extremities were normal. The cervical lymph nodes were slightly enlarged, the others not.

He was treated with iron and arsenic. Dr. Torrey wrote October 29, 1899, three months later, that the spleen was no longer palpable.

Dr. Torrey examined him again in December, 1902. The boy was then in good health, but still somewhat pale. The spleen was not enlarged.

Case XXVI.—Wolff S., aged thirteen months, was admitted to the Infants' Hospital March 14, 1899. He had always been improperly fed and had always suffered from disturbances of digestion.

He was poorly developed and nourished. The fontanelle was 6 cm. in diameter. There was a marked rosary. The heart and lungs were normal. The liver was palpable almost as low as the umbilicus in the right nipple line. The spleen was palpable at the level of the umbilicus. The epiphyses at the wrists and ankles were enlarged. There was a moderate anterior bowing of the tibiæ. There was a moderate general enlargement of the lymph nodes.

He was seen August 7, 1902, three and one-half years later. At that time he was perfectly well. The liver was normal. The spleen was not palpable. There was no enlargement of the lymph nodes.

Case XXVII.—Max S., aged twenty-two months, was seen at the Outpatient Department of the City Hospital in February, 1897. He had been very sick with diarrhea during the summer of 1896. The abdomen had been distended, and Dr. Deering had found an enlarged spleen. He had had more or less disturbance of digestion since that time, and a few weeks before coming to the hospital had had a sharp attack of fermental diarrhea, from which he was recovering.

He was well developed and nourished and moderately pale. There was a slight rosary, but no other evidences of rickets. The liver was normal. The spleen was palpable about 5 cm. below the costal border. The blood was not examined at that time.

He was seen again in May, 1897, three months later. At that time he was in very good condition and of good color. The tip of the spleen was just palpable. The blood at that time showed hemoglobin, 105 per cent.; red corpuscles, 5,160,000; white corpuscles, 5000; small mononuclear, 30 per cent.; large mononuclear, 1 per cent.; polynuclear neutrophiles, 62 per cent.; eosinophiles, 7 per cent. There was very little variation in the size of the red corpuscles, but none in their shape. No nucleated forms were seen.

THE RELATION OF ENLARGEMENT OF THE LIVER TO THAT OF THE SPLEEN.

In estimating the size of the liver in infancy it must be remembered that it is normally proportionately larger than in adult life. While under normal conditions it usually does not extend more than 2 or 3 cm., it may extend as much as 4 cm. below the costal border. Only six of the livers in this series were larger than this (11, 15, 16, 17, 20, 21). Two (17, 20) of these cases had congenital syphilis. In general the largest livers were associated with the largest spleens. In three (18, 19, 22) of the five (18, 19, 20, 21, 22) cases, however, in which the spleen reached to the anterior superior spine the liver was not enlarged. Enlargement of the liver was, therefore, evidently not dependent upon that of the spleen nor enlargement of the spleen on that of the liver.

THE RELATION OF ENLARGEMENT OF THE LYMPH NODES TO THAT OF THE SPLEEN AND LIVER.

There was a general enlargement of the lymph nodes in every case in which their condition was noted. The greatest enlargement was found in cases in which the spleen was much enlarged (14, 15), but they were moderately enlarged in a case in which the spleen was only slightly enlarged (4), and they were only slightly enlarged in three (19, 21, 22) of four cases (19, 20, 21, 22) in which the spleen was the largest. There was no evident relation between the size of the lymph nodes and that of the liver. They were much enlarged with both normal (14) and enlarged (15) livers, and slightly enlarged with both normal (2) and enlarged (21) livers. The enlargement of the lymph nodes could not have been due, therefore, to that of the spleen or liver. Enlargement of the lymph nodes is, moreover, almost invariably found in all conditions of malnutrition in infancy. Hence it must be regarded here, as elsewhere, merely as a manifestation of malnutrition.

THE RELATION OF THE NUMBER OF RED CORPUSCLES AND THE AMOUNT OF HEMOGLOBIN TO THE SIZE OF THE SPLEEN.

The number of red corpuscles bears no constant relation to the size of the spleen. This is evident if the cases are arranged according to the number of red corpuscles and compared with the arrange-

ment according to the size of spleen. The arrangement according to the number of red corpuscles, beginning with the largest number, is 13, 11, 8, 10, 5, 3, 16, 15, 17, 19, 22, 20, 21, 7, 12, 18, 2, 14, 4, 6, 1, 9. The two smallest counts were in two cases in which the enlargement of the spleen was slight (9, 1); the largest, 5,800,000, was in a case (13) in which the spleen reached to the umbilicus. In five cases (5, 10, 8, 11, 13) there were over 5,000,000 red corpuscles, while in five others (3, 15, 16, 17, 19) there were over 4,000,000. The lowest count in the cases in which the spleen reached to the anterior superior spine (18) was 3,556,000, while the lowest in those in which the spleen reached to the umbilicus (14) was 2,553,000.

There was no evident relation between the number of red corpuscles and the size of the liver.

The diminution in the amount of hemoglobin was always relatively greater than that in the number of red corpuscles. The hemoglobin, however, is always relatively low in infancy, and a relatively great diminution in the amount of hemoglobin is characteristic of the anemias of infancy. The color index in these cases bears no relation to the size of the spleen or liver.

THE RELATION OF THE NUMBER OF WHITE CORPUSCLES TO THE SIZE OF THE SPLEEN.

The arrangement of the cases according to the number of white corpuscles, beginning with the minimum, is as follows: 6, 2, 14, 1, 21, 11, 18, 17, 13, 10, 8, 3, 20, 12, 5, 4, 7, 19, 9, 22, 15, 16. Accepting 14,000 as the normal limit of white corpuscles, there was no leukocytosis in eight (6, 2, 14, 1, 21, 11, 18, 17). Four of these cases (14, 17, 18, 21) were among those in which the spleen was largest. Of fourteen cases in which the number of white corpuscles was increased, the spleen was but little, or moderately, enlarged in seven (3, 4, 5, 7, 8, 9, 10), and much enlarged in seven (12, 13, 15, 16, 19, 20, 22). The largest leukocytosis (47,220) was in a case in which the spleen reached to the umbilicus (16) and the next largest (31,500) in another case in which the spleen reached to the umbilicus (15); but in one case in which the spleen reached to the umbilicus (14) there were only 8200 white cells, and in the case with the next to the largest spleen there were only 10,700.

It is evident that there was no constant relation between the

number of leukocytes and the size of the spleen. The largest spleens were sometimes unaccompanied by leukocytosis, and there was sometimes a marked leukocytosis when the spleen was only slightly enlarged. The largest leukocytoses were usually found, however, in connection with the largest spleens.

THE RELATION OF THE NUMBER OF WHITE CORPUSCLES TO THE SIZE OF THE LIVER.

There was no evident relation between the size of the liver and the number of white corpuscles. There were only 10,700 white cells in the case with the largest liver (21), while the two cases in which the leukocytosis was largest showed only a slight enlargement of the liver (15, 16). Leukocytosis was also marked in cases with normal sized livers (9, 22).

THE RELATION OF THE NUMBER OF WHITE CORPUSCLES TO THE SIZE OF THE LYMPH NODES.

There was no evident relation between the size of the lymph nodes and the number of white corpuscles. In the two cases in which the enlargement of the lymph nodes was greatest (14, 15) there were 8200 and 31,500 white corpuscles, respectively. There were moreover, 47,220 white corpuscles in a case in which the enlargement was slight (16).

THE RELATION OF THE NUMBERS OF RED AND WHITE CORPUSCLES TO EACH OTHER.

The numbers of red and white cells have no constant relation to each other; for example, in one case (16) there were 4200 white, and 1,736,000 red cells, and in another (2) 4800 white and 3,288,000 red. In one case (16) with 4,408,000 red corpuscles there were 47,220 white, while in another (17) with 4,200,000 red there were only 13,400 white corpuscles.

THE RELATION OF THE MORPHOLOGIC CHANGES IN THE RED CORPUSCLES TO THE OTHER SIGNS.

In a very general way the degree of the morphologic changes varied with the number of red corpuscles, the more marked changes occurring in the cases with the smallest numbers of red corpuscles. There were many exceptions to this rule, however. The changes were, on the whole, more marked in the cases with leukocytosis.

There was no correspondence between the degree of the morphologic changes and the size of the spleen. The morphologic changes were most marked in four cases (1, 6, 7, 9), in which the spleen was not much enlarged, and in four (12, 15, 19, 22) in which the spleen was much enlarged.

The morphologic changes varied, therefore, rather with the number of red and white corpuscles than with the size of the spleen; that is, they formed a part of the pathologic changes in the blood and were not connected with those in the spleen.

Certain peculiarities are worth noting. In some cases the morphologic changes were marked while there was a comparatively slight diminution in the number of red cells. Nucleated cells were present in cases in which there was little or no diminution in the number of red corpuscles; for example, normoblasts with 5,158,000 red corpuscles (10), and megaloblasts with 4,340,000 (15) and 4,000,000 (19) red corpuscles. In several of the cases which recovered (12, 18, 19) large nucleated red corpuscles were very abundant. These changes are, of course, merely examples of the tendency of anemia in infancy to revert to the fetal type of blood.

There was no correspondence in the amount of the enlargement of the liver and of the spleen. There was no correspondence in the degree of enlargement of the lymph nodes and of the liver and spleen. There was no constant relation between the diminution in the number of red corpuscles and the size of the spleen and liver. There was no constant relation between the number of leukocytes and the size of the spleen and liver, although the largest leukocytoses were usually found in connection with the largest spleens. There was no constant relation between the number of leukocytes and the degree of enlargement of the lymph nodes. There was no constant relation between the number of red and white corpuscles. The morphologic changes in the red corpuscles did not vary with the size of the spleen, but in a very general way, with many exceptions, with the number of red and white corpuscles, showing that they were a part of the pathologic blood condition and not connected with the condition of the spleen. The degree of the morphologic changes was in a general way a guide as to the severity of the anemia. Very marked changes did not necessarily point to a fatal outcome, however, as several cases (12, 18, 19) in which they were most marked recovered. They

merely show the tendency of the blood in the anemias of infancy to revert to the fetal type. The hemoglobin was always relatively low, as it almost always is in the anemias of infancy. The condition of the blood in cases 23 and 24, in which there was no enlargement of the spleen, shows that there is nothing characteristic about the blood changes found in infancy in association with splenic tumor. The conclusion seems justified, therefore, that the enlargement of the spleen, liver and lymph nodes developed independently of each other, and that they were not directly connected, either as cause or effect, with the changes in the blood.

Granting that this conclusion is correct, the association of these conditions suggests that they are all the results of some common cause.

ETIOLOGY.

Rickets was present in all but two of the cases (6, 9). Neither of these had very large spleens, but they ranked first and third as regards the severity of the anemia. The rachitic changes were slight in eleven (1, 2, 3, 5, 7, 12, 14, 15, 17, 20, 21), moderate in six (4, 8, 11, 13, 18, 22), and marked in three (10, 16, 19). The enlargement of the spleen and changes in the blood were considerable in two (16, 19) of the three cases in which the rachitic changes were marked, but no greater than in other cases (15, 21) in which they were slight. It is evident, therefore, that the rickets was not the direct cause of these pathologic conditions, but was itself a symptom of some common cause. Further evidence that rickets was not etiologically responsible for these conditions is the fact that 80 per cent. of the children under two years of age at the clinic from which these cases were taken show more or less marked signs of rickets, while these conditions are comparatively rare.

Disorders of the gastroenteric tract were present in every case in which data were obtained. In two of those without data the food had been unsuitable. There was a history of improper food in all but four (2, 3, 13, 14) of the cases with data on this point. These cases were fed on the breast, and all had gastroenteric disturbances. It is probable, therefore, that in these cases too the food, even if it was breast milk, was unsuitable. Diseases of the gastroenteric tract, whether or not due to improper food, are not always followed by anemia and enlargement of the liver and spleen, and therefore can-

not be the direct cause of these conditions. Disorders of the gastro-enteric tract do, however, always cause disturbances of nutrition, and it is to these disturbances of nutrition that they probably owe their etiologic importance.

Two (17, 20) of the cases had syphilis. It was in both associated with rickets, improper food and gastroenteric disturbances. No special importance can be attributed to it, therefore, as a general etiologic factor. It undoubtedly acts chiefly by disturbing nutrition.

Prematurity and pertussis, each present in one case (7, 9), probably acted in the same way.

Disturbances of nutrition in infancy may produce various results. Rickets and scurvy are undoubtedly peculiar manifestations of disturbances of nutrition. In other instances disturbances of nutrition produce atrophy, anemia or enlargement of the lymph nodes, liver or spleen. Why disturbances of nutrition in one case cause rickets, in another atrophy, and in another anemia or enlargement of the lymph nodes or spleen is not known. The fact that they do cause all these various conditions explains the peculiar combinations in which these conditions are found and their evident independence of each other.

CONCLUSIONS.

It seems justifiable to conclude, therefore, that when anemia, splenic tumor and enlargement of the liver or lymph nodes are found in association in infancy they are in no way dependent on each other, but are all manifestations of a common cause—disturbance of nutrition; that there is nothing characteristic about the blood changes found in association with enlargement of the spleen, as similar changes are found when there is no enlargement of the spleen; that the anemia is secondary rather than primary; that there is no justification for placing the cases of anemia in infancy associated with enlargement of the spleen or liver in a class by themselves and calling it "anemia infantum pseudoleukemica," or "splenic anemia of infancy," that these terms should be dropped from our nomenclature.

PROGNOSIS.

The ultimate fate of these cases is of some interest. Seven disappeared from view after a short time; two (12, 16) of these probably died; five (5, 7, 8, 17, 20) probably recovered; two (17, 20) of these were syphilitic.

Seven are known to have died; one (13) of meningitis, and six (1, 3, 6, 9, 15, 22) without complications. They died after three days, five days, one month, one month, two months, and seven months. The blood changes were marked in all of these cases. They included most of the severest cases. The spleens were very large in three (13, 15, 22), but comparatively small in the others.

One (12) was doing well after eight months. Seven (4, 10, 11, 14, 18, 19, 21) were well after six months, seven months, seven months, eighteen months, two and one-half years, six years, seven years. The blood changes were moderately severe in these cases. Nucleated reds were numerous in five, megaloblasts predominated in two. Nucleated red corpuscles and megaloblasts are, therefore, evidently not of so much importance in prognosis in infancy as in later life. Five of these cases (12, 14, 18, 19, 21) were among those with the largest spleens, and two (10, 11) of the others had considerably enlarged spleens. Two of the largest spleens were not palpable after seven and eight months (21, 12). Others were found absent after seven months (11), eighteen months (19), two and one-half years (4), and seven years (18). One (10) was just palpable after six years. In three cases in which the spleen was much enlarged, although the blood was not examined, it was not palpable after three months (25), five months (27), and three and one-half years (26). One (21) very large liver was of normal size after seven months, another (11) moderately enlarged; one was still slightly enlarged after seven months. The improvement in the blood condition during recovery is seen in cases 19 and 27.

The prognosis in these cases depends, therefore, more on the condition of the blood than on the size of the spleen. Recovery may take place even when the changes in the blood are very severe. The size of the spleen has no influence on the prognosis. The largest spleens may return to the normal size in a few months.

No.	Spleen.	Liver.	Glands.	Red corpuscles.	Hb.	White corpuscles.	Small mononuclear.	Large mononuclear.	Polynuclear neutrophiles.	Eosinophiles.	Myelocytes.	Morphologic changes.	Etiology.					Results.
													Rickets.	Syphilis.	Improper food.	Gastroenteric disorders.	Miscellaneous.	
1	1	4	?	1,250,000	15%	10,300	67.0	2.0	29.0	2.0	...	Marked.	+	...	Yes	Yes	.....	Died in one month.
2	2	N.	+	3,288,000	42%	4,800	49.0	5.0	45.0	1.0	...	One normoblast to one macroblast.	+	...	Breast	"	.....	Lost in one month; probably died.
3	2	N.	+	4,519,000	57%	15,900	44.0	3.5	47.0	5.5	..	Slight; normoblasts.	+	...	"	"	.....	Died in seven months.
4	2 × 5	N.	+ +	2,296,000	25%	16,850	4.4	19.6	44.4	0.4	1.2	Moderate; six normoblasts to one megaloblast and one microblast.	++	...	Yes	"	.....	Well in two and one-half years; spleen not palpable; liver normal.
5	2 × 4	3	?	5,072,000	65%	16,600	40.0	18.0	41.0	1.0	...	Slight.	+	...	"	"	.....	Lost; probably did well.
6	3 × 4	N.	+	1,736,000	25%	4.200	69.0	5.0	25.0	1.0	...	Marked.	0	...	"	"	.....	Died in one month.
7	3 × 6	N.	+	3,708,000	30%	18.520	31.0	4.0	64.0	1.0	...	Marked; normoblasts.	+	...	"	"	Premature.	Lost in one month; probably did well.
8	3 × 4	3	+	5,380,000	65%	15,625	43.0	2.0	54.0	0.5	0.5	Slight.	++	...	?	?	.....	Lost in two weeks; probably did well.
9	3½	N.	+	950,000	19%	27,000	52.0	13.0	32.0	0.5	2.5	Marked; twenty-four normoblasts to twenty-one megaloblasts and eight microblasts.	0	...	?	?	Pertussis.	Died in five days.
10	4 × 8	N.	+	5,158,000	68%	15,200	51.0	5.0	40.0	4.0	...	Moderate; occasional normoblast.	+++	...	Yes	Yes	.....	Well in six years; spleen just palpable; liver normal.
11	4	6	+	5,650,000	75%	11,800	32.0	8.0	51.0	9.0	...	Slight.	+ +	...	?	?	.....	Well in seven months; spleen not palpable; liver 4½ cm. below ribs.
12	Umb.	2	+	3,564,000	60%	16,250	31.0	8.0	60.0	1.0	...	Marked; megaloblasts.	+	...	?	Yes	.....	Alive in eight months; doing well; spleen not palpable; liver normal.

+ = slight. ++ = moderate. +++ = marked.

No.	Spleen.	Liver.	Glands.	Red corpuscles.	Hb.	White corpuscles.	Small mononuclear.	Large mononuclear.	Polynuclear neutrophiles.	Eosinophiles.	Myelocytes.	Morphologic changes.	Etiology.					Results.
													Rickets.	Syphilis.	Improper food.	Gastroenteric disorders.	Miscellaneous.	
13	Umb.	3	+	5,800,000	?	15,000	43.0	2.0	55.0	...	...	.....	+¬	...	Breast	Yes	.....	Died soon; meningitis.
14	Umb.	3	+++	2.553,000	55%	8,200	44.0	4.0	50.0	1.0	1.0	Moderate.	+	...	"	"	.....	Well in six months; spleen? liver?
15	Umb.	5	+++	4,340,000	60%	31,500	29.5	9.9	56.5	0.3	3.8	Very marked; eleven normoblasts to eighty-nine macroblasts; nuclear figures.	+	...	Yes	"	.....	Died in two months.
16	Umb.	5	+	4,408,000	58%	47,220	36.5	9.5	50.5	1.0	2.5	Moderate; thirteen normoblasts to eighteen macroblasts and one microblast.	+++	...	"	"	.....	Lost; probably died.
17	Umb.	6	++	4,200,000	65%	13,400	42.0	11.0	45.0	2.0	...	Moderate.	+	Yes	"	"	.....	Lost; probably recovered
18	A. S. S.	N.	?	3,556,000	60%	12,400	28.0	10.0	55.0	7.0	...	Moderate; megaloblasts most numerous.	++	...	"	"	.....	Well in seven years; spleen? liver?
19	A. S. S.	3	+	4,000,000	40%	18,750	34.4	12.6	51.0	0.2	1.8	Marked; sixteen normoblasts to nine megaloblasts.	+++	...	"	"	.....	Well in eighteen mos.; spleen not palpable; liver, 3 cm. below ribs.
20	A. S. S.	5	++	3,750,000	55%	16,200	50.0	6.0	39.0	5.0	...	Slight.	+	Yes	"	?	.....	Lost in two weeks; probably recovered.
21	A. S. S.	+++	+	3,720,000	65%	10,700	30.0	4.0	65.0	1.0	...	Slight.	+	...	"	Yes	.....	Well in seven months; spleen not palpable; liver, 3 cm. below ribs.
22	A. S. S.	3	+	3,750,000	50%	29,600	30.0	18.0	48.0	2.0	2.0	Marked; eight normoblasts to twelve macroblasts and seven microblasts.	++	...	"	?	.....	Died in three days.

+ = slight. ++ = moderate. +++ = marked.

DISCUSSION.

DR. OSLER: This group of cases, studied by Dr. Morse, brings out the fact of the great frequency of enlargement of the spleen in the malnutrition of children. I do not think any of the cases of anemia, so-called, of adults begin as early as the second year. Some begin as early as the fifth or sixth year, and they belong to a different group of cases from those here referred to. It is very interesting to note the frequency of cirrhosis of the liver in conditions of malnutrition among children in the tropics, particularly in India.

SUDDEN DEATH AND UNEXPECTED DEATH IN EARLY LIFE, WITH ESPECIAL REFERENCE TO THE SO-CALLED THYMUS DEATH.

By J. P. CROZER GRIFFITH, M.D.,
PROFESSOR OF DISEASES OF CHILDREN, UNIVERSITY OF PENNSYLVANIA.

The term "sudden" may be used to indicate a death occurring in from a few seconds up to a few hours at the utmost, while "unexpected" may be conveniently applied in this connection to the deaths taking place somewhat more slowly and yet entirely unexpectedly in patients who had previously shown no alarming symptoms or any reason why a fatal issue need be apprehended. Occurring in either of these methods, death is not infrequent at any age, but is especially common in the first two years of life. West reported 627 instances, at all ages, collected in London in 1854 (Brouardel[1]). Of these, 272 occurred in children under five years old, and in 126 of these the infant was not yet one year old. Richter[2] reported 1797 cases of sudden death in children up to the age of fifteen years occurring during five years. Of these 1525 were in the first year. The causes are rather different at this early age, however, from those operating in adult life. In later years we find sudden death from such causes as valvular heart disease, angina pectoris, and apoplexy predominating. In infants, on the other hand, more prominent among the causes are convulsions, syncope, and especially diseases of the respiratory apparatus.

Doubtless all of us have met with cases in our practice among young children in which death occurred suddenly and very unexpectedly. The reason has often been very obscure or entirely undiscovered. Even an autopsy has revealed nothing in the way of explanation. The child may have appeared to be perfectly well and then died suddenly. In other instances death perhaps has occurred unexpectedly during some disease in which we had no reason to dread a fatal issue, at least at the time. In still other cases it is probable that

some condition was operative which, although overlooked by the mother, was of a nature which would have been evident to a physician had one been present. In any event, as the occurrence is most disturbing to the parents, and possibly a cause of reflection by them upon the physician, the matter is worthy of study apart from the natural scientific interest which pertains to it.

We cannot pass in review all the possible causes, but must limit ourselves to some of the more prominent or most interesting of them. The low resisting power of infants and the great excitability of the nervous system are the principal reasons for the occurrence of sudden death at this age. Conditions affecting the *respiratory apparatus* are generally, and with good reason, considered to hold the most prominent etiologic place. *Coryza* occurring in the newborn may rarely be the cause of sudden death by what has been described as aspiration, or swallowing, of the tongue. By the violent efforts at breathing through the mouth the tongue is drawn backward and its inner surface and tip become pressed against the hard palate, cutting off more or less the entrance of air. Death in the same way is said occasionally to occur in young infants with pertussis. Doubtless this accident is not of so frequent occurrence as was formerly supposed, yet apparently death does undoubtedly take place at times in this way, and perhaps oftener than we imagine. Bouchut[3] was the first to call attention to this. He has observed it several times, and details an interesting case in a child of three weeks where breathing had been badly obstructed by coryza and where death occurred. Henoch[4] describes two cases of the same nature. In one of these instances in order to relieve the condition it was necessary to keep the tongue drawn forward by a catgut thread passed through its tip.

Asphyxia from overlying is a cause of sudden death in infancy which has long been recognized. I may call to your mind, for instance, the judgment of Solomon between the two mothers, one of whom had overlain her own child and claimed as hers the living child of the other. In view of the interest possessed by death from suffocation from a medicolegal standpoint, it is important to bear in mind that asphyxia from overlying, or from direct smothering with criminal intent, is undoubtedly of very much less frequency than has been commonly supposed. Most infants believed to have died in this way probably owed their death to other causes. We must remember that

weakly, and especially premature, children, born with a certain degree of asphyxia, are exceedingly prone to suffer from a fatal relapse after the physician in attendance has supposed that all danger was over. The necessity of constant watchfulness for days in these cases is very great.

Undoubtedly *spasm of the glottis* has appeared to be one of the most prominent and startling causes of sudden death, especially in those infants who have been in apparently perfect health. It may be that we have been warned by previous attacks of laryngeal spasm. In other cases there has been nothing to indicate the danger. The spasm depends on the very great irritability of the nervous system, oftenest seen in debilitated or rachitic children, but sometimes occurring quite independently of such conditions. It is probable that many cases of death attributed to other causes in reality depend upon this. Perhaps still oftener, however, death only *seems* to be the result of laryngospasm, but in reality is dependent upon syncope. There is reason to believe that this is true of many, or even of most, of the cases of death attributed to laryngospasm. This will be referred to again later. I may detail the following interesting history of a case of sudden death from what appeared to be spasm of the larynx :

Case I.—H. G., aged seven months. Admitted to the Children's Hospital, Philadelphia, January 6, 1902. The history was of a very vague character, the child's mother, who could speak little English, saying that the "child died every day." The child had a convulsion in the receiving ward, and another the same night in the hospital ward, the latter of very short duration.

The examination showed a well-nourished child, with the heart and lungs exhibiting nothing abnormal; the fontanelle too large and too prominent; blue veins over the scalp; no teeth; beaded ribs; abdomen distended and the veins over it prominent; the spleen not felt, probably owing to the distention. There was also a slight tendency to abdominal tache.

No further symptoms, however, were manifested, and the general condition was excellent until January 12th, when at 5.45 P.M. the child, without apparent cause, became cyanosed and stiff, and respiration and the action of the heart ceased. It immediately became relaxed, the cyanosis disappeared, and the pupils became dilated, but the heart failed to respond to active stimulation, and artificial respiration and oxygen were of no avail. During the illness the temperature was about 98°, with occasional rises to 100°.

The characteristic features of the clinical history were the presence of well-developed rickets, and the repeated occurrence of laryngospasm before entrance into the hospital.

The autopsy was of particular interest. It showed the subcutaneous fat well preserved, the blood very dark, the lungs almost airless and deeply cyanotic, the thymus gland hypertrophied, red, with the two lobes overlying the heart, hiding it from view, and extending downward to the diaphragm. It measured 8½ cm. in length, 4⅓ cm. in breadth, 1 cm. in thickness, and weighed 21 grams. There was no evidence of compression by the thymus of the surrounding structures. The trachea was patulous; the mediastinal and bronchial glands slightly enlarged; the liver of normal size, slightly fatty; the spleen enlarged, weighing 34 grams. Peyer's patches were very prominent and the mesenteric glands were enlarged and very numerous, but not caseous. Tubercle bacilli were found in the latter on microscopic examination. The kidneys were dark and slightly lobulated.

The characteristic feature of the autopsy was the general lymphatic enlargement, especially of the thymus gland.

Another very similar case may be detailed:

Case II.—S. L., aged six months, admitted to the Children's Hospital, February 6, 1903, for convulsions. The child had been having convulsions at irregular intervals since January 1, 1903, and seemed in the intervals to be fretful and cried a good deal of the time. On February 8th he was noticed to be somewhat rigid, with the thumbs held in the position of tetany. Examination on this morning showed a well-nourished child with the head rather rachitic in shape and with rather large fontanelles; some veining of the scalp and at the root of the nose; a moderate degree of beading of the ribs; no enlargement of the wrists; the abdomen somewhat distended with gas; the spleen not felt; a few coarse râles in the chest. No convulsions occurred, but the child did not look well, and on February 11th commenced to vomit its food with considerable force immediately after taking it. On the afternoon of February 13th the child looked better and slept some hours. On waking from sleep at 3 P.M. he exhibited slight twitching of the face, and then immediately developed intense jactitation, as though unable to breathe. A few ineffectual efforts at respiration took place, and the heart beat very feebly and intermittently, and in a few moments death occurred. There was no rigidity or general clonic movements in the attack. Slight fever had been present since the day of entrance.

The autopsy showed the external lymphatic glands of the body slightly enlarged, and the subcutaneons fat well preserved. The tonsils were decidedly enlarged, and the glands at the base of the tongue slightly so. There was slight hypostatic congestion of the lungs; the bronchial and mediastinal lymph nodes were moderately enlarged; the heart appeared normal; there were numerous enlarged glands in the mesentery. The lymphatic tissue of the intestines was hyperplastic. The spleen was moderately enlarged, deep red in color, with the Malpighian bodies increased in number and size. The liver was slightly enlarged; the kidneys normal. The most interesting feature was the condition of the thymus gland. This organ occupied the upper

third of the mediastinum and extended downward over the base of the heart, the lower third of it more or less surrounding the great vessels. It measured 7½ cm. in length and 4 cm. in breadth at its widest portion. There was no evidence that it exerted any pressure upon the trachea or other organs.

The main features of note in both cases were the presence of rickets, the history of convulsions, the sudden death, and, at the autopsy, the decided widespread hypertrophy of the lymphatic tissue of the body, and especially of the thymus gland.

In both these cases the condition during life and at and after death corresponds entirely with the condition found in the much-discussed "thymus death." Cases of this nature and under this heading have been reported many times in literature, and much has been written for and against the possibility of the occurrence of death due to enlargement of the thymus gland. The literature on the subject is large, and the controversy has been at times very active. An extended review of the whole subject would be of little value in this connection, as it would but repeat what has been well done by others, notably Friedjung,[5] in an exhaustive and able critical review. Only a very brief review of the subject can be given.

As early as 1614 Plater[6] called attention to the fact that the thymus was often found enlarged in cases of sudden death. After that the connection was repeatedly referred to, and in 1830, after writings by Kopp,[7] the belief in the existence of a thymic asthma due to an enlargement of the thymus became general, and the identity of this with laryngospasm was accepted. The extensive investigations of Friedleben[8] overthrew the earlier views completely. He denied the existence of a thymic asthma, or of any relation between the thymus gland and laryngospasm, and upheld his position so successfully that his views were generally accepted. This state of things continued, and only a few writers held to the earlier views until Grawitz[9] directed renewed attention to the possibility of compression of the trachea by an enlarged thymus, and detailed two cases of sudden death which he attributed to this cause. Many others followed his lead with cases purporting to be instances of death from pressure, until Paltauf[10] advanced his theory of the influence of the lymphatic constitution, or the "status lymphaticus," in the production of sudden death. According to this view, accepted by Escherich[11] and followed by many others, the enlargement of the thymus, as of other lymphatic tissues of the

body, is but the anatomic manifestation of a certain disordered constitutional state of a lymphatic chlorotic nature, which so influences the nervous system that sudden death may occur from the cessation of the heart's action, brought on by very slight and varied causes.

The whole subject is in a state of discussion still, and it seems impossible to reach as yet any final conclusions. At least it seems certain that it is possible for a much enlarged thymus to compress the trachea—or perhaps the heart, large vessels, or recurrent laryngeal nerves—and produce death. A case was reported by Siegel[12] from Rehn's clinic, in which there was increasing dyspnea apparently from pressure upon the trachea. Tracheotomy was without avail. The jugulum was then incised, and the thymus found and anchored to the edges of the wound, the symptoms being at once relieved. A very similar case of relief was reported by Koenig,[13] and still another by Perrucker.[14] A certain small number of cases has been published in which there seemed at the autopsy no doubt that the trachea, the large vessels, or the nerves had been compressed during life. Thus in a case of Marfan's,[15] a child aged two and a half months exhibited symptoms during twenty-four hours or more before death ; and at the autopsy the trachea was found almost completely flattened by a very large thymus gland. Other cases of death apparently due to compression are those of Clessen,[16] Kruse and Cahen,[17] Kohn,[18] Flügge,[19] Biedert,[20] Abelin,[21] and others. However, in the great majority of cases attributed to pressure there has existed no real evidence either during life or at the autopsy that death was actually produced in this way. This is true, for instance, of the cases reported by Grawitz,[9] Lange,[22] and d'Oelsnitz.[23] It has been *assumed* merely that because the thymus was found enlarged death must have resulted from its pressure. But if the death is one from pressure on the trachea, the symptoms should have come on more slowly, with increasing difficulty of respiration, not relieved by tracheotomy. This is, however, not the usual history. It is characteristic of the truly sudden " thymus death " that the child has previously been in good health or entirely free from alarming symptoms, and has then died quite suddenly as though from laryngospasm or heart failure. To meet this difficulty, the view has been advanced repeatedly that the thymus, already hyperplastic, undergoes, for reasons not understood, a sudden congestive swelling, or possibly a sudden increase in size dependent upon its own secretion,

and that this gives rise to the pressure symptoms and the immediate fatal ending, which is aided, too, by any bending backward of the head, since this narrows the space occupied by the thymus gland and the adjacent structures. Beneke[24] reported three cases of sudden death in which he believes that this bending backward was a prominent factor. It is true that the space between the manubrium sterni and the vertebral column is very small—1 to 3 cm. at two years of age (Pott[25]), 2 cm. at eight months (Jacobi[26])—and that the sudden swelling of the thymus could readily produce pressure symptoms. But for the view, convenient as it is, that such swelling does or can occur, there is still lacking either anatomic or physiologic proof. Friedleben has shown that the bloodvessels of the thymus gland are comparatively few in number and small, and that no considerable enlargement of the gland through congestion could be produced by experiments on animals. Again, although he shows that under certain influences enlargement may follow from the secretion of the gland, he states that there is no proof that this is of such a sudden and considerable nature that pressure symptoms can result.

With reference to the existence of the so-called status lymphaticus as an entity and its relation to sudden death only this much can be admitted without question, viz., that in a large proportion of cases dying supposedly of layngospasm the thymus gland has been found enlarged. The enlargement is not, as a rule, great. Friedleben states that out of seventy-five such cases there were only seven in which the thymus was above an average size. Nevertheless the statistics also show, as Biedert[20] points out, that large thymus glands are commoner than small ones in cases of laryngospasm ; so that after all some connection may exist. Richter,[2] on the other hand, found what he recognized as the status lymphaticus with much enlarged thymus in only one of his 1797 cases of sudden death. Thus sudden death can occur without enlargement of the thymus; and it is noteworthy, too, that in many cases where the thymus had been found to be abnormally large, neither a sudden death nor a slower death with distinct pressure symptoms had taken place. Thus, in a child aged six months coming under my care in the Children's Hospital and seen at the same time as the infant S. L., the death took place after several days of vague symptoms, the most prominent being failing heart strength, cyanosis, a semicomatose condition, and

a difficulty in swallowing, depending apparently upon the mental state or the great weakness. The autopsy showed a widespread bronchopneumonia of a lobar type of both lungs, and an enlaged thymus gland, weighing 12.88 grams, and almost identical in size and in appearance with that seen in the previous case (S. L.), but with little enlargement of other lymphatic tissue except the spleen. In these cases the symptoms were absolutely different from those of the "thymus death," and death evidently resulted from pneumonia.

As regards the possible hyperthymization of the blood, or some other form of autointoxication arising from a hyperplastic gland, a theory suggested by Escherich,[11] and emphasized by Svehla,[27] this does not seem to be supported by any clinical evidence. Thiemich,[28] Ganghofner,[29] and others express themselves strongly against it.

One fact does, however, remain clear—that there is a certain constitutional anomaly seen in some children, and even in adults, which predisposes to sudden death from trivial causes. It is true that enlargement of the thymus and of other lymphatic tissue is very often seen in these cases, but whether these are accidental accompaniments or not is uncertain. If they are accidental, as seems very probable, then the lymphatic system has nothing to do with the matter, and the name "status lymphaticus," as applied to the constitutional condition, is a misnomer. In other respects, however, Paltauf's views are supported by much clinical evidence and are shared by many writers. The only question is whether the constitutional anomaly rests upon an anatomic basis, either of the lymphatic organs or of others.

This constitutional disturbance depends on a state of faulty nutrition. Not that there is any wasting of the child, but that the condition of metabolism is in some way at fault. It is attended by pathologic disturbances of the nervous centers, giving this system an extreme irritability. The nerves controlling the action of the heart are, of course, involved, as are also to some extent those controlling respiration. It is on this account that many cases suffering from this anomaly exhibit a tendency to repeated attacks of true laryngospasm. The final sudden exitus appears, however, not to be due to spasm of the larynx, although it may so seem, but to a sudden cardiac paralysis, as pointed out by Escherich,[11] Pott,[25] and others. This appears to be true of the cases I have detailed, the heart having ceased to beat at the beginning of the attack.

The true laryngospasm is probably seldom fatal. In 425 cases of what had been designated as spasm of the larynx, Soltmann[30] found a mortality of but 11 per cent. It is extremely likely that many or most of these fatal cases owed the fatal issue to cardiac failure. Very slight causes are sufficient to produce this sudden cardiac death. Slight traumata are often sufficient, such as the giving of a hypodermic injection, or the puncture test for a pleural effusion. The much quoted Langerhan's case of death after the injection of antidiphtheric serum is believed by Escherich,[11] with reason, to belong to this category. Many sudden deaths during general anesthesia doubtless belong here also, as do the sudden deaths of persons in bathing, as reported by Nordmann[31] and others, and the interesting cases of death after applications to the skin, such as the use of lead-water, mentioned by Ranke,[32] and the packing in salicylic acid solution, reported by Escherich.[11]

The condition is a neurosis, but it is not necessarily the so-called status lymphaticus, as Ganghofner[29] has pointed out, and as I have already mentioned. The lymphatic overgrowth may probably exist without the neurosis, and vice versa, although it is probable that they are generally combined. So, too, rickets is very frequently present also, for the reason that the disturbances in the nutritional condition are liable to produce all three conditions.

The symptoms of sudden death in these cases are very characteristic and very uniform. Often the child has appeared entirely well. In many cases, however, there is a puffy or pasty, anemic appearance, and not infrequently the patient is rachitic. Enlargement of the lymphatic tissue of the body may or may not be found. In the great majority of the cases the death is entirely unexpected, and not preceded by any indications of danger. Very often the child is found dead in bed. In other cases there has been striking restlessness before the symptoms immediately attending death have commenced. These final symptoms have been well described by Pott.[25] The child suddenly throws back its head, makes noiseless, gasping efforts at respiration, and rolls its eyes upward. The pupils dilate; the face becomes cyanotic and swollen; the tongue is cyanotic, greatly swollen, caught between the jaws and pressed against the hard palate. The veins of the neck stand out as thick cords; the hands are clenched, with the thumbs in the palms and the forearms strongly pronated and

adducted; the lower extremities are extended, and the toes adducted and dorsally flexed; the spinal column is arched. There occur slight twitching movements of the face and a few unavailing efforts at inspiration. The convulsions then stop at once, the face becomes ashy, the cyanosis lessens, and in, at most, one or two minutes death occurs. The action of the heart ceases at the beginning of the attack.

I may report another very interesting case in which death seemed to the attendants to have taken place on two occasions before the fatal issue really occurred. In the absence of an autopsy we do not know with certainty whether the thymus was enlarged or not.

Case III.—Marie U., born November 16, 1900. When two months old, in January, 1901, while having her nose sprayed with an atomizer she suddenly stopped breathing and became blue in the face. She was carried immediately to the Children's Hospital, which was close by. Sylvester's method of artificial respiration was employed, together with oxygen and stimulation. It was only after ten minutes that respiration was again established. From this time on she was troubled with accumulation of mucus in the throat, which appeared at times to interfere with nursing, causing her to choke, although never in a suffocating manner. Any violent attack of crying, however, was liable to bring on a momentary suffocative attack, apparently of the nature of brief laryngospasm. Her general nutrition was only fair, and she cried a great deal, probably the result of hunger. There appeared also to be obstruction to respiration through the nose, which probably accounted for much of the difficulty in nursing. There was also much flatulence.

Under careful management of her diet her weight steadily increased. She was weaned entirely at the age of five months, and continued to gain and to be in very fair health, except for a constant disposition to keep her mouth open, as though adenoid growths were present. At the age of six or seven months she passed successfully through a severe attack of pneumonia, apparently croupous in nature. When a little over a year old, January, 1902, having been apparently well previously, she was taken to a neighbor's house by her mother. While returning she developed difficulty in breathing, became blue, and then ceased to breathe entirely. The attack appeared to be the result of exposure to the cold air. She was again taken to the Children's Hospital, which was fortunately nearby. The same methods were employed as before, but apparently without success, and she was considered dead. Finally, however, by the use of Sylvester's method of artificial respiration and by the administration of oxygen, with hypodermic injections of whiskey, she recovered by the end of fifteen minutes, respiration starting of its own accord, and the child's color became normal. From this time she continued in very fair health, except for the positive presence of large adenoid growths, which, however, Dr. Walter J. Freeman, who saw her at the time, feared to remove on account of the suffocative attack at the time when the nose was sprayed.

Examination in February, 1902, showed a slight dulness over the upper sternum, indicating possibly an enlargement of the thymus gland, but not being at all conclusive. In July, 1902, she suffered from a slight attack of scurvy.

At the end of October, 1902, being now nearly two years old, she developed a bronchitis. A day or two later she developed considerable fever and a remarkable degree of jactitation, with some increase of the rapidity of respiration, although without any other special evidence of dyspnea in the form of heaving of the chest or moving of the alæ. No physical signs of pneumonia could be found. By the next morning she was greatly worse; pale, slightly cyanotic, with numerous scattered râles in the chest. By afternoon she was taken into the Children's Hospital, where, in spite of inhalations of steam, the use of atropin, and other appropriate treatment, she grew rapidly worse, and died within twenty-four hours from the time of the onset. No autopsy was permitted.

The cause of death in this case may possibly have been a rapidly developing bronchopneumonia. Yet the impression at the time was that the child was smothering, in spite of our inability to find in the lungs a satisfactory explanation for this. Pressure by an enlarged thymus may perhaps have existed, but the case is very similar to that of Kohn,[18] in which there was the same great restlessness, and pneumonia was suspected. The thymus gland in his patient was found enlarged at the autopsy, yet there seemed to be no proof that death occurred from pressure. In this case as well as in my own it is probable that death was due to heart failure, depending on the neurosis already described, and that the status lymphaticus may have been combined with it.

Sudden death may occasionally occur in *pertussis* as a result of bronchopneumonia, or oftener of a spasm of the larynx. Ducastel[33] and others have reported cases of this nature. Death from aspiratio linguæ in this disease has already been referred to. Death may also occasionally take place in infants from *expiratory apnea*, as Kassowitz denominates it.

What is probably a central involvement of respiration sometimes occurs and ends fatally. Sometimes this is seen in children who have the neurotic tendency which might in some cases lead to laryngeal spasm. In such instances the child dies almost instantly, as though from heart failure, and indeed, in some cases, probably from this. In other cases respiration becomes more and more rapid without other symptoms, and without discoverable cause, and the infant dies in a few hours. It may take place in the course of some other illness, or

in children not previously sick. An interesting case of this nature, in which the child recovered from a desperate condition, has been reported by Westcott.[34] The following instance, in a patient seen with Dr. Herbert P. Fisher, illustrates this condition :

Case IV.—Wellington H., aged ten months. In July, 1899, he suffered from a disturbance of the bowels in which, although there was diarrhea, the evidence of constitutional involvement appeared by far the most prominent symptom. The stools were offensive, green, not very frequent, and contained some mucus. The child appeared to be improving steadily, when he developed an unnatural drowsiness, with slight fever and extremely rapid respiration; the most rapid, Dr. Fisher says, that he has ever seen in any child. There was no cyanosis, and the pulse was not rapid in comparison with the respiratory rate. The child refused nourishment, and lay perfectly quiet except for the rapid breathing. This condition developed in the afternoon and continued more or less during the night with little improvement. Toward morning large watery stools were passed, the result of a purgative given, and the rate of respiration rapidly returned to normal, leaving the child pale and weak, but wonderfully improved at the time when I saw him.

In this instance, although death did not occur, yet it was so imminent that the case may well be used to illustrate the danger of a fatal ending from a central respiratory involvement, the nature of which is not clear.

I may report still another instance in which, unfortunately, the issue was not so happy.

Case V.—Baby D., aged six months. First seen December 19, 1900. The child was at that time in an extremely wasted condition, starving upon a food which was insufficient to support life, yet which had appeared to be the only thing it could take without vomiting or diarrhea. On very careful feeding the baby steadily improved, was bright and apparently entirely convalescent except for an occasional tendency to looseness of the bowels. By the end of February it had gained three pounds in weight. After that there was an inconsiderable loss, with rather more frequent movements. On March 11th the child was slightly colicky, yet looked well, and I told the parents that I had no further anxiety about it. In the late afternoon of the 12th it still looked well, and the parents had noted nothing amiss. I observed, however, that the respiration was decidedly too fast. No fever, cough, or labored breathing was present, and nothing abnormal could be found in the chest. In the next few hours the child failed with extraordinary rapidity the respiration growing more rapid and shallow. The child died suddenly in the early morning hours of the 13th before a physician could be summoned. Percussion of the chest after death showed nothing abnormal. There was no autopsy.

The diagnosis in this case was a respiratory failure from intestinal toxemia, no other cause seeming to suggest itself.

The rapid development of *bronchopneumonia* may sometimes kill with apparent suddenness, the attendant having noticed no symptoms, or the gravity of the symptoms being entirely overlooked. This is of very common occurrence in the newborn. Probably the majority of cases of sudden, or, at least, rapid and unexpected, death at this age are due to this cause.

Sudden death from *heart failure* is not uncommon in early life. This is not infrequently seen in infectious diseases, especially diphtheria, due to changes in the heart muscle, or to the influence of toxins in the blood. It may also occur in debilitated states, or in respiratory diseases, especially pleural effusion, as a result of too sudden a movement, improper position, or excitement. I recall a case of severe diarrhea in an infant of less than a year, in which collapse, followed by death in little more than half an hour, appeared to have been precipitated by the careful raising of the infant into the sitting position for the purpose of examining the lungs. Sudden cessation of the heart's action may take place also in cases of acute nephritis on account of the strain which increased arterial tension has thrown upon the heart. So, too, stopping of the heart may occur as the result of distant nervous influences. Thus it is possible that the sudden death in healthy children which has occasionally followed sudden movement or excitement, as, for instance, tossing the child into the air, has been caused by inhibition of the heart's action. As we know, however, that excitement of this nature is well capable of producing spasm of the larynx, it is equally possible that the death may have been due to the latter. In fact, many cases of sudden death placed in other classes might with propriety be considered as due to heart failure.

Sudden death in children known to have *organic heart disease* is probably not so common as in adult life. It may, however, occur where we do not expect it. The following case is an illustration of this fact:

CASE VI.—B. S., aged three years. Admitted to the Children's Hospital on November 21, 1901, for genu valgum, the result of well-marked rickets. She developed a scarlatinal rash and was sent home five days after admission. The family physician pronounced it a "baby rash," and the child was readmitted to the hospital about December 2d, to be operated on for bow-legs. She had

become apathetic and drowsy, and in a few days desquamation was discovered on the body and albumin and casts in the urine, and the child was again sent home on account of danger to other patients. Her heart at the time showed nothing abnormal. On January 11, 1902, she was readmitted. Examination showed slightly cyanosed lips, rapid breathing, some dyspnea and cough, and a few râles in the lungs. The urine did not contain albumin. A double murmur was heard at the cardiac apex, with accentuated aortic and pulmonary second sounds. On January 14th, at 9 A.M., after seeming very bright and not at all ill, her heart suddenly ceased beating and failed to respond to stimulation. The only other symptom present was the fact that she had vomited five times during the previous night.

The autopsy showed a considerable amount of clear fluid in each pleural cavity, with some hypostatic congestion of the lungs. The pericardial sac was much distended with clear fluid without evidence of recent pericarditis, but the pericardium was firmly adherent to the upper portion of the right auricle. The endocardium of the right auricle was yellow and fibrous; the lining of the other chambers and of the valves was apparently normal. Death appeared to have been due more to hypertrophy and dilatation of the heart than to the existence of actual valvular lesions.

Sudden death in infants with *asthenia* is of comparatively frequent occurrence. It happens often that an infant who has been ill in bed, in apparently the same weakly condition which has lasted for days or weeks, will unexpectedly be found to have died without any change of symptoms to account for this. This is especially common in cases of premature birth. The autopsy often shows no lesions whatever. An instance of this inexplicable sudden death is the following:

CASE VII.—Helen Elizabeth M., aged nine and three-fourths months in June, 1902. She had suffered severely from whooping-cough, possibly complicated by pneumonia, several months before. She had recovered from this, but was always underfed, and had not been gaining in weight. There was a constant moaning cry, and the child was evidently starving. Under a carefully regulated diet she steadily and rapidly improved. I had felt all uneasiness about her disappearing, when I was told that she had been taken out in her coach one morning, apparently well, and then died suddenly without discoverable cause. The abdomen is said to have been somewhat swollen on the morning of the day of death, but to no greater a degree than she frequently experienced. There is said to have been slight edema present a few days before death. The weight of the baby when completely dressed with clothes for outdoors was only a little over nine pounds.

It is a noteworthy fact that these wasted infants sometimes gain in weight shortly before death occurs. In such cases the gain may be due to a degree of general edema, depending upon the feeble cardiac power.

I have already alluded to many cases of death, which evidently depend upon disordered states of the nervous system, although exerting their influence upon some special region of the body, as, for instance, in spasm of the larynx, heart failure, etc. Still another very common cause of sudden death included among nervous affections is *convulsions*. These are, after all, only a symptom, and are in many cases rather the attendant than the cause of the fatal issue. *Hyperpyrexia*, due, of course, to the influence of some agency upon the nervous centers, is a not infrequent and very unexpected cause of death, very rapid even if not actually sudden, occurring in children who have been perfectly well or only slightly ailing but a few hours before. This may be seen in heat-stroke in infants and in malignant eruptive fevers, and very frequently in pneumonia. As a rule, a general convulsive condition attends death in such cases. The following case, one of heat-stroke, seen in consultation with Dr. W. K. Evans, illustrates this point:

Case VIII.—James A. H., aged two years and eleven months. On July 14, 1900, he suffered from slight diarrhea. By July 15th he had recovered entirely. On the 17th he was exposed to prolonged heat while playing in the sun during the afternoon of a very hot day. Slight diarrhea followed with a temperature of 100.4° and symptoms suggesting cerebral involvement. On the morning of the 18th the bowels were somewhat better; the abdomen still tender and tympanitic. The child seemed irritable and did not wish to be lifted from the sofa, where he lay persistently on the right side. The temperature was 101°. By afternoon of the same day the condition was much the same. By the next day the symptoms were improved in every particular, and by the 20th still more so, and the child seemed practically well. On the 21st there was a relapse with some vomiting and a return of diarrhea. The mental state became heavy. The child felt the intense heat of the weather very much, and sponging and stimulants were used repeatedly. There was no vomiting and the action of the heart was good. By 5.30 the temperature had risen to 106°, and unconsciousness with convulsions developed. The temperature was reduced, but rose by 8 o'clock to 108°. An ice-pack reduced the temperature to 100°, but consciousness was not recovered. The temperature again rose rapidly, attained 108° by midnight, and death took place shortly after.

Death in this case was entirely unexpected. There were really no bad symptoms of any kind until the late afternoon of the last day of life, when the convulsive and comatose condition developed. The extreme elevation of temperature at 8 o'clock was entirely unsus-

pected. We were about to give a warm bath for the convulsions, when the thermometer revealed that cold water and not hot was urgently needed. These cases of heat-stroke in infants are common. I have seen them repeatedly.

Another case may be related, showing the unexpected death depending on hyperpyrexia in pneumonia.

Case IX.—Baby V., aged three and a half months, had been suffering for a short time from whooping-cough, which was not particularly severe. Examination of the chest had revealed what had hitherto not been suspected —that the child was also the subject of congenital heart disease. The physical signs were very positive, the murmurs being loud, yet the baby exhibited no cyanosis. In June, 1896, the child suddenly developed slight physical signs of pneumonia, convulsions, and a rise of temperature to 108°. Cold baths were employed and the temperature fell to the neighborhood of 100°. The convulsions ceased, but the child remained weak, and died in an hour or two after the onset of the critical symptoms.

Of course, neither of these cases is at all uncommon. I have detailed them merely as illustrations of a condition too often seen.

Convulsions are, of course, due to many other causes than hyperpyrexia. Nervous reflex irritability of various parts of the body may be responsible. All of us, unfortunately, are doubtless rich in experience of sudden death from convulsions in the case of children about whom neither we nor the parents had had the slightest anxiety.

To be classified in diseases of the nervous system are probably those cases in which death takes place in marantic states, apparently due to the *depressing effect of chilling*, or to a fall of bodily temperature without discoverable cause.

Congenital syphilis is a not infrequent cause of sudden death even in infants which appeared perfectly healthy. This has been emphasized especially by Fournier.[35]

Rarely asphyxia may result from the *rupture of a caseous bronchial gland* or a *retropharyngeal abscess* into the respiratory tract. This latter has been reported in a good many cases. The symptoms of an abscess of this kind are apt to be overlooked by one who is not familiar with them, and death may take place very suddenly if the abscess ruptures. In other instances death results from *pressure of intrathoracic growths* or enlarged glands upon the pneumogastric nerve. The *aspiration of food* into the windpipe has been assigned as a cause

of sudden death. Parrot (quoted by Brouardel[1]) has reported a number of such cases. The occurrence probably takes place much less often than has been supposed, and only in the weakest infants in which the ability to cough has disappeared. It seems very likely in the cases where a curd of milk has been found in the windpipe that it has reached this position only because the child was in the act of dying when the final vomiting took place. The same is true of asphyxia from the *entrance of ascarids into the larynx.* Although death has been repeatedly ascribed to this cause, in most instances it is probable that the worms entered the respiratory tract after death. A very interesting case has, however, recently been reported by Wagner,[36] in which there was no doubt that the sudden death was the result of suffocation from a cluster of ascarides obstructing the glottis.

Gastrointestinal affections seldom occasion sudden death in early life. A number of cases are reported by Bouchut[3] and others where sudden death appeared to have been induced by large numbers of ascarids in the intestines. It is probable, however, that this is of rare occurrence.

Various *malformations and accidents* not already mentioned may also produce death. Among these are perforation of the intestines, entrance of foreign bodies into the larynx or trachea, injury from forceps, strangulated hernia, external hemorrhage from the stomach or bowels, and internal hemorrhages, especially in the newborn. Meningeal hemorrhage is the most frequent form of this latter, but other regions may suffer. I may close with an interesting instance of an entirely unexpected death from hemorrhage.

Case X.—Baby C., female, born June 7, 1902. Owing to a contracted pelvis on the part of the mother, the child was delivered presumably at the eighth month, although its well-developed state after birth renders it probable that some mistake was made regarding the exact stage of pregnancy. Labor was rendered difficult only by a remarkable degree of uterine inertia, which made podalic version necessary. The after-coming head was delivered, however, largely by internal effort. There was a moderate amount of asphyxia present immediately after birth, relieved promptly, however, in a few seconds, and never returning. Everything was favorable during the five days of life, except considerable colic, with a slight difficulty in nursing from the breast, apparently not due in any way to lack of strength. On the night of the fifth day of life the child cried a great deal, apparently as a result of colic; it was fed in the early morning, became quiet, and was laid

down asleep in good condition. Shortly afterward, when again lifted, it was found to be breathing its last.

An autopsy showed the peritoneal cavity apparently nearly full of fresh blood. Dr. Alfred Hand, Jr., who made the examination, estimated roughly that "nearly a pint must have been lost." The source of the hemorrhage could not be discovered.

The cause of the hemorrhage in this case is difficult to discover. Sepsis not infrequently occasions widespread hemorrhage in the newborn. There was, however, no evidence of this condition here. In other cases the accident is due to strain put upon bloodvessels during difficult delivery. It seems probable that the case was of this nature. The hemorrhage may take place, primarily, directly into some organ, or secondarily, by bursting from some abdominal organ into the peritoneal cavity. The suprarenal bodies are, perhaps, the most frequent site of primary hemorrhage.

BIBLIOGRAPHY.

1. Le Mort Subite, 264.
2. Münchener med. Wochenschrift, October 14, 1902.
3. Maladies des Nouveau-Nes, 1885, 8th edition, 279.
4. Kinderkrankheiten, 1895, 8 Auf., 128.
5. Centralblatt f. d. Grenzgeb. d. Med. u. Chir., 1900, iii. 465, 523, 587.
6. Observat. in homin. affect. pleurisque., libri iii., 1614, 172.
7. Deukwürdigkeiten, 1830, i.
8. Die Physiol. d. Thymusdrüse, 1858.
9. Deutsche med. Wochenschrift, 1888, xiv. 429.
10. Wien. klin. Wochenschrift, 1889, No. 46; 1890, No. 9.
11. Berliner klin. Wochenschrift, 1896, 645.
12. Ibid., 887.
13. Zentralbl. f. Chirurg., 1897, xxiv. 605.
14. Gaz. Hebd. de Méd. et de Chir., 1899, 695.
15. Soc. Méd. des Hôpitaux, 1894, xi. 361.
16. Münchener med. Wochenschrift, 1898, xlv. 330.
17. Deutsche med. Wochenschrift, 1890, xvi. 450.
18. Ibid., 1901, 22.
19. Vierteljahrsch. f. gerichtl. Med., 1899.
20. Berliner klin. Wochenschrift, 1896, 581.
21. Journal f. Kinderkr, 1870, lv. 107.
22. Jahrb. f. Kinderheilk., 1898, xlviii. 119.
23. Bull. de la Soc. de Pediat., January 26, 1902.
24. Berliner klin. Wochenschrift, 1894, 216.
25. Jahrb. f. Kinderheilk., 1892, xxxiv. 118.
26. Transactions Association American Physicians, 1888, iii. 299.
27. Wien. med. Blatter, 1896, xix. 723.
28. Vierteljahrsch. f. gerichtl. Med., 1901. xxi. 300
29. Münchener med. Wochenschrift, 1902, 1728.
30. Calmus "Zur Pathol. u. Therap. des Laryngo-spasmus," 1889.
31. Correspondb. f. Schweizer Aerzte, 1889, 202.
32. Münchener med. Wochenschrift, October 14, 1902.
33. De la Mort par Access de Suffocation dans la coqueluche, Paris, 1872.
34. Archives of Pediat., 1897, 753.
35. La Sem. Méd., 1901, xx. 54.
36. Deutsche med. Wochenschrift, 1902, 886.

DISCUSSION.

Dr. Blumer: I have had the opportunity of seeing nine cases of so-called "thymus death" in the last four or five years, and I think the cases can be divided into two classes: those in which the organs are practically sterile at autopsy, and those in which there is infection.

In some cases the condition simply predisposes the individual to death from infection. In one case, although the patient had appeared in perfect health and died suddenly, there was found a general streptococcus infection. In another case with tetanus, due to a pistol-shot wound, death occurred with unusual rapidity. The other cases were sterile at autopsy, and they showed histologic lesions that were very suggestive. They consisted in changes that were limited almost exclusively to the lymphatic system in the form of proliferation in the germinal centers. The lesions in the spleen suggested those found in diphtheria. On studying these lesions more clearly I think they can be distinguished from lesions found in the various infectious diseases. They do not show the extensive necrosis that occurs in the infectious processes. They are suggestive in connection with the recent work done by Flexner upon the lymphotoxins. There is a very close resemblance between these lesions and the lesions of his lymphotoxic cases. Where the case is sterile it may be an instance of autointoxication with the lymphotoxins.

Dr. Jacobi: The thymus has undoubtedly something to do with a number of sudden deaths by pressure in infancy. In other cases they are a part of the general disintegration resulting from atrophy. There are other cases of a different character altogether. They occur in very young children, between five and eight months of age. These sudden deaths occur in the first stage of a laryngismus stridulus, viz., that of apnea. The children do not live long enough to develop the second stage, viz., the crowing inspiration. All of these children, forty-nine out of fifty, have craniotabes, with the accompanying hyperemia of the meninges and of the brain, and more or less edema.

NOTE ON TYPHOID FEVER AND SCARLET FEVER, WITH SPECIAL REFERENCE TO THE DIAGNOSTIC VALUE OF BLOOD CULTURES.

By LUDVIG HEKTOEN, M.D.,
OF CHICAGO.

(From the Memorial Institute for Infectious Diseases.)

This brief communication is written for the purpose of calling attention to two points, first, the possibility of mistaking typhoid fever for scarlet fever on account of early rash and angina, as well as the possible coincident occurrence of these two diseases in the same person; and, secondly, the value of bacteriologic examination of the blood in determining in such cases the existence of typhoid fever.

Recent investigations have shown that in the early stages and during the height of the attack of typhoid and paratyphoid fever the specific bacilli occur in the blood so constantly and in such numbers that they are readily demonstrable by cultural methods. Such appears to be the case also at the beginning of relapses in typhoid fever (Schottmüller, Ruediger). In many respects this is the most important recent advance in our knowledge of these diseases, and bacteriologic examination of the blood according to the modern methods of several inoculations of 1 c.c. or so of blood into many times that quantity of medium, constitutes the most valuable diagnostic measure of these fevers at the periods mentioned. Repeatedly have bacilli been demonstrated in the blood many days before the appearance of specific agglutinins.

According to Curschmann[1] the concurrence of scarlet fever and typhoid fever has been described by Taupin, Murchison, Glaser, and Eichhorst. In Murchison's and Glaser's cases scarlet fever seems to

[1] Nothnagel's Specielle Pathologie u. Therapie, 1898, B. iii., i. Theil, 303–304.

have developed in the second or third week of typhoid fever, and Curschmann remarks that most frequently in this association the development of scarlet fever is secondary. In the following case it is reasonable to believe that scarlet fever and typhoid fever developed very nearly at the same time. At all events the onset, the angina, the rash, the tongue, and the desquamation were quite distinctive of scarlet fever; and the demonstration of typhoid bacilli and of specific agglutinins in the blood, as well as the subsequent course of the disease, leave no room for doubt as to correctness of the diagnosis of typhoid fever.

Case I.—(135.) Woman, aged twenty-two years, married, housewife, was admitted to Dr. Baum's service in Ward No. 26, Cook County Hospital, on October 12, 1902.

The history (Dr. Otradovee) states that she was taken suddenly ill three days before admission with nausea, malaise, headache, pain in the limbs. The throat began to swell, became red, and deglutition was difficult on account of pain. On the following day a rash appeared on the neck and body, spreading to the limbs and face. The examination at the time of admission showed a diffuse erythematous rash on the neck and body, face and limbs. There was a deep subcuticular flush with raised points. The tonsils were enlarged and swollen, but without membrane; there was a strawberry tongue.

On the 14th cultures of the blood were made, and the typhoid bacillus developed in pure growth. The serum was then strongly agglutinating for typhoid bacilli.

On the 15th it is noted that typical scarlatinal desquamation was going on.

On the 18th the spleen was palpable; there were numerous raised spots on the abdomen; quite frequent bleeding from the nose occurred; headache persisted; bowel movements frequent.

Recovery took place after a typical typhoid course, the temperature falling to normal about the twenty-first day.

It must be granted that the skeptic might find room for questioning the correctness of the diagnosis of scarlet fever in this case. As stated, the onset, the angina, the rash, the tongue, and the desquamation seemed distinctive of scarlet fever, but in the absence of absolutely conclusive evidence, such, for instance, as would be furnished by the demonstration of the etiologic agent, one could not successfully disprove the claim that all the symptoms were caused by the typhoid fever; but general desquamation does not seem to occur, at least in the lighter forms of typhoid erythema. In his valuable paper on

"Anomalous Eruptions in Typhoid Fever" before this Association the late Dr. Da Costa[1] states that the scarlatiniform eruption in typhoid passes away without desquamation. The occurrence of desquamation in this case seems to me, therefore, to support strongly the diagnosis of scarlet fever.

It may have been cases of this kind that gave rise to the following description by Thomas of "scarlatina with a course similar to typhoid fever," which I give word for word with von Jürgensen's comments as translated in the American edition of the latter's work on scarlet fever in Nothnagel's *System*.

"By no means seldom occurs still another form of the disease characterized by slight or moderate localizations and by disproportionately severe and very long-drawn-out fever. The latter feature, together with the considerable intensity of the pyrexia, warrants the term 'scarlatina, with a course similar to typhoid fever.'

"Evidently in this form the fever is of major, and the local affection of minor, importance, although at times nothing more than a protracted local disturbance appears to cause the continuation of the fever into the fourth week and longer.

"The *eruption* in this form of scarlatina appears usually after a hyperpyrexia of several days' duration, which follows a sudden initial fever. It is often unusually slight; otherwise it develops according to rule. The *angina* is second in importance of the local affections, and is also frequently of no consequence. It is, as a rule, present in advance of the exanthema. Notwithstanding these facts, *brain symptoms and fever*, especially in the beginning of the disease, are not infrequently quite marked; the expression is vacant, thirst severe, and the tongue tends to dryness, yet clearing itself in a characteristic manner. Some cough may be present, and the skin, which after the fading of the exanthema has desquamated as usual, remains dry and hot. Later the patient is apathetic and, in addition to some slight affection of the organs of hearing, is usually deaf. The spleen swells somewhat, *hypostasis may occur in the lungs*, and the bowel movements are of the nature of a diarrhea. As a rule, no local affection other than a moderate enlargement of the cervical lymphatic glands is perceptible in connection with the remittent fever of weeks' duration."

Von Jürgensen adds: "Nephritis may appear in the third week, and, according to Thomas, determines, when present, the character of the fever.

"At the autopsies of the subjects dying in the latter periods of the disease one notes, besides the usual involvement of the phraynx, the lymph glands, the skin, and perhaps also the kidneys, 'hyperemia of the brain, slight tur-

[1] Transactions of the Association of American Physicians, 1899, xiv., 89–98.

bidity of the meninges, catarrh of the air-passages and pulmonary hypostasis, transudations into the serous cavities, the liver and spleen full of blood and often swollen, marked floccular involvement of the intestinal tract, and infiltration of its mesenteric lymph glands; sometimes also Peyer's patches are swollen in a manner rather similar to typhoid fever.'

"It is by no means certain that in these cases there is a real complication with enteric fever."

The last remark by von Jürgensen, it would seem, probably does not state the cases correctly; it may well be that in some, at least, of these cases there is a real complication with typhoid fever. And, as shown by Jochmann's recent case, a paratyphoid bacillemia may complicate scarlet fever.

Jochmann[1] reports a secondary infection with a paratyphoid bacillus in a girl, aged seven years, with undoubted scarlet fever, ending in death on the sixteenth day. Cultures from the blood on the fifteenth day gave few colonies of streptococci and numerous colonies of paratyphoid bacilli. This result was obtained again after death. There were no special intestinal lesions. In this case there seems to be little or no reason to doubt the diagnosis of scarlet fever—the onset was sudden, with vomiting and tonsillitis, followed by a pronounced eruption, marked enlargement of the cervical glands, and on the ninth day desquamation.

In the two other cases that I report it probably concerns instances of early angina and erythema in typhoid fever.

CASE II.—(175.) E. G., single woman, aged twenty-six years, suffered from headache and backache for three or four days, feeling now chilly and then again warm. On the fifth day she remained in bed; about this time she noticed a distinct rash, and there was pain in the throat. With this history she was brought to the Hospital of the Memorial Institute for Infectious Diseases and admitted by the interne as a case of scarlet fever. At the time of admission there was a faint rash on the chest. The cultures of the blood showed pure growths of the typhoid bacillus which was agglutinated by the patient's serum. This serum also agglutinated in high dilution stock cultures of typhoid bacillus. The patient was transferred to the Presbyterian Hospital and passed through an uncomplicated attack of typhoid fever of moderate severity, ending in recovery. There was no desquamation.

CASE III.—(238.) J. H., trained nurse, aged twenty-seven years, entered Ward 26, Cook County Hospital, January 23, 1902, with the diagnosis of scarlet fever. According to the history (Dr. Snyder) the illness began rather

[1] Centralbl. f. Bakt., Referate, 1903, xxxiii., 8–9.

suddenly, although the patient had not been feeling wholly well for some time before, becoming easily tired and not having as good an appetite as formerly. This she traced to her being on night duty. The actual onset of the attack is described as marked by headache, backache, and prostration. This continued for fully two days, during which she remained on duty, but in the evening of the second day she was forced to go to bed on account of the intensity of headache and backache; there were now present also anginal symptoms; the face was flushed, and there was noted by the nurse who looked after the patient a generalized erythema which seemed to be typically scarlatinal. The pharynx was congested, but there was no membrane. The temperature at this time was 103.8° F. On the following morning, January 23, she entered the service of Dr. Baum in Ward 26. Examination shows a well-nourished and well-developed young woman; she is somewhat exhausted, but not in any special distress, and clear mentally. On the neck and chest is a diffuse red rash with punctiform spots. Mouth and lips dry; tongue brownish, fissured. Tonsils prominent; faucial pillars congested; no membrane. The cervical glands appear a little large. Thoracic organs apparently normal. The patient complains of tenderness on palpation of the abdomen, most marked in the right iliac region; the abdominal walls are somewhat rigid. Spleen not palpable. Blood cultures were made January 26, three days after admission, five drops of blood being added to each of two flasks containing 50 c.c. plain bouillon. In both there developed pure growths of typhoid bacillus. This bacillus was agglutinated by typhoid serum. A few days later the patient's serum was found to agglutinate typhoid bacilli. The patient passed through a severe attack of typhoid fever ending in recovery. She did not desquamate.

The patient gave a history of measles and whooping-cough and exposure to scarlet fever when a child, while an older sister was sick with that disease; but the mother does not think that she had any eruption.

In these two cases I have taken it for granted that there was not sufficient evidence in either one to warrant the diagnosis of scarlet fever. Yet, if we assume that mild cases of scarlet fever occasionally may not be followed by desquamation, the claim that in both these instances it actually concerned scarlet fever associated with typhoid fever, perhaps could not be disproven with absolute success. So long as it is not possible to place the diagnosis of scarlet fever upon an absolute etiologic basis there always must be more or less room to question the real nature of scarlatiniform diseases, especially in patients not giving a clear history of previous attacks of typical scarlatina.

In neither of these cases was it possible to obtain any information of the use by the patients of any drugs that might have caused the misleading rashes.

Text-books in general mention the occasional presence of erythema in typhoid. Osler says: "It is not very uncommon in the first week of the disease to find a diffuse erythematous blush—E. typhosum. Formerly we thought it might be due to quinine."[1] Eichhorst[2] cautions against mistaking the diffuse typhoid erythema occasionally seen on the chest and abdomen, more rarely on the extremities, for scarlatina. This mistake he says is especially likely to occur when angina[3] is present. According to Curschmann,[4] Jenner (who mentions a case of typhoid fever mistaken for scarlet fever), Raymond, Le Maigre, and others have described scarlatiniform eruptions in typhoid fever. These eruptions Curschmann is inclined to regard as medicamentous in nature.

But the most important statement that I know of concerning scarlatiniform and other anomalous rashes in typhoid fever is the aforementioned article by Da Costa. He points out that the scarlatiniform rash may remain throughout the fever, but this is rare; it may come out late, even in convalescence, and return in relapse; for the most part it is connected with angina. It passes away without desquamation. "Save under the exceptional circumstances of attending sore-throat and desquamation, there is no difficulty in determining the two diseases or in diagnosing that scarlet fever is not intercurrent in typhoid." Da Costa also discusses a more uncommon measles like rash in typhoid fever, and details a case of the intercurrence of true measles in typhoid. Finally, he mentions the combination and interchangeability of the scarlatiniform and the measles like rashes in enteric fever.

The special point that I wish to emphasize again is that the practically constant presence of typhoid bacilli in the blood in the early stages, during the height and at the beginning of relapses of typhoid fever, renders it possible by the use of proper cultural methods to settle promptly the diagnosis of typhoid fever in peculiar cases like those now reported. The indications are that this statement also holds true in paratyphoid fever.

[1] Osler, 4th edition, 1902, p. 17.

[2] Handbuch, 1891, iv., 382.

[3] The occurrence now and then of angina in the beginning of typhoid fever suggests that the tonsils may be one port of entrance of typhoid bacilli into the blood.

[4] Loc. cit., p. 114.

THE INFLUENCE OF THE DIFFERENT VARIETIES OF FAT ON THE FORMATION AND EXCRETION OF ACETONE.

A Preliminary Report.

By E. P. JOSLIN, M.D.,
OF BOSTON.

Two years ago a case of diabetic coma was reported before this Association (Transactions of the Association of American Physicians, 1901) which was remarkable for the fact that the total quantity of acetone, diacetic and β-oxybutyric acids excreted in the last three days of life exceeded that hitherto recorded. It seems probable from the work of Magnus-Levy, Geelmuyden, Schwartz, von Noorden, and others that the acid intoxication in diabetic coma has its origin in the fat of the food or that already stored up as such in the body. The following experiments were undertaken to obtain further evidence on this point, and to learn, if possible, which one of the three common fats in the food contribute most to the acidosis.

Various objections arose to an experimental study of this nature in diabetic individuals. For this reason advantage was taken of the fact that an acid intoxication of moderate severity occurs in starvation. Accordingly the acetone in the urine and breath of a healthy individual during two days of starvation was estimated as a control. After complete recovery from the effects thereby produced the acetone was again estimated in the same person during similar periods and under similar conditions, except that the subject ate definite quantities of oleic, palmitic, and stearic acids, sodium palmitate, tristearin, and triolein.

The last meal was taken at 6 P.M., and the experiment began at 11 or 1 at noon on the next day. During the twenty-four hours preced-

ing the commencement of eight of the experiments the acetone was estimated in the urine. The average quantity for this period was 10.6 mg. On the first day of starvation the average amount of acetone in the urine rose to 145.5 mg. and on the second day to 375.5 mg. in two controls. During the same period the acetone in the breath was 87 mg. and 469 mg., respectively. In the first control the total acetone in urine and breath for the first day was 269 mg. and for the second day 900 mg.

Oleic acid was given in two experiments. In one of these 104 g. and in the other 90 g. were taken during the two days. A marked effect was at once seen. The total quantity of acetone was 382 mg. and 596 mg., respectively, on the first day, and 1205 mg. and 1773 mg. on the second day.

Stearic and palmitic acids had no influence on the excretion of acetone when given in similar quantities, but the absorption of these substances was very incomplete. Sodium palmitate, on the other hand, acted quite the same as oleic acid, but as only 37.8 g. were absorbed the effect of its action must probably be attributed to the sodium it contained.

Triolein and tristearin also failed to have any effect on the excretion of acetone. This may be due to the glyceryl radicle in these substances, which, being oxidized, prevents the formation of acetone.

The results of the work so far emphasize the necessity of caution in the change of the diet of diabetics from food poor in fat to one which contains large amounts.

TUBERCULOSIS OF THE TONSILS AND THE TONSILS AS A PORTAL OF TUBERCULOUS INFECTION.

By HENRY KOPLIK, M.D.,
OF NEW YORK.

The tonsils have long been a subject of investigation as a seat of tuberculosis, and the literature is quite voluminous on this theme. Orth and Cohnheim first called attention to the fact that these organs might not only be the seat of tuberculosis, but that they were potent factors in the dissemination of this infection throughout the body. The observations on tuberculosis of the tonsils and the conclusions drawn from them differ, because one set of observers has studied the disease from a purely clinical standpoint, while another has analyzed pathologic and autopsy material. Pluder and Fischer examined a number of hypertrophied tonsils excised from the living subject. Any conclusions drawn from such material must necessarily be imperfect, for concealed tuberculosis elsewhere in the body would escape confirmation. Tuberculosis of the tonsil may be a primary isolated process unaccompanied by tubercular foci elsewhere. This is exceedingly rare, the only case of the kind in the later literature is that of Friedmann. In this case the patient was aged one year and four months; the tonsil alone was affected, the child dying of other causes. Other authors (Orth, Ruge, Schlessinger, Scheibner, Kruckmann) speak of primary tuberculosis of the tonsil with accompanying tuberculosis of the cervical lymph nodes. In these cases the disease was limited to these organs, or may have spread thence and then involved other organs. In one case published by Ruge the tuberculosis involved the tonsil and lymph nodes of the neck and caused also secondary cervical spondylitis, the lungs having escaped. Other cases are published by Schlenker, Brugmann, Friedmann, and Orth, in which the tonsillar affection was the starting point of an acute miliary tuberculosis or of a chronic pulmonary tuberculosis of the lung. The secondary forms

of tuberculosis of the tonsil are very common (Strassman, Ruge, Dmochowski, Schlenker). The victims of chronic pulmonary tuberculosis sooner or later develop tonsillar infection. This form of tonsillar tuberculosis is only of passing interest. In both the primary and secondary forms of tuberculosis of the tonsil the cervical lymph nodes are quite constantly affected. Children furnish by far the greatest quota of cases, not only of primary tonsillar tuberculosis, but the form of the disease in which the tonsil draws into the infection the cervical lymph nodes. In some cases the tonsil is, to external appearances, normal; in others it may be hypertrophied (Lewin, Pluder, Fischer), the external surface showing no erosions or ulcerations. In a few cases the affected tonsils were even atrophied (Walsham). These atrophied tonsils when examined were found, as in the other forms mentioned, to contain tubercle tissue and tubercle bacilli. Ulcers on the tonsil of a tuberculous nature have only rarely been observed. In all the forms the cervical lymph nodes may be enlarged. When such is the case the largest nodes and those supposedly infected are found high up behind the tonsil. The affected nodes form a packet, stretching from behind the angle of the jaw along the great vessels toward the clavicle. The youngest diseased nodes are found behind the great vessels in chains. They are often very numerous. The cases of primary tuberculosis of the tonsil confirmed by autopsy in the later literature may be summarized as follows:

One case mentioned in this paper of isolated tonsillar tuberculosis in a young child observed by Friedmann. The other two cases, by the same observer, of tonsillar tuberculosis with involvement of the cervical lymph nodes. Two cases in children, by Krueckmann, with tuberculosis of the cervical lymph nodes. Two cases by Schlenker of tuberculosis of the tonsil and the accompanying lymph nodes in adults. Four cases of sixty examined by Scheibner of possible primary tuberculosis. One case by Ruge, mentioned above, in a girl of eighteen years. Pluder and Fischer, on the other hand, examined the tonsils of thirty-two patients which had been excised for hypertrophy and found tuberculous infection in five; Lartigau and Nicoll found 10 per cent. of eighty-five adenoids the seat of tuberculous tissue and tubercle bacilli. These were mostly in children, the tonsils alone being examined. The other organs clinically revealed no tuberculosis. The authors give a résumé of 161 cases of Lermoyez, Gottstein and Brindel

examined in the same way. In nineteen of these cases the tonsils were found to be tuberculous and to contain tubercle tissue and bacilli. In those cases in which the excised tonsils alone have been examined the diagnosis of primary disease of the tonsil must necessarily be only provisional. In this respect such investigations must remain incomplete. It must be admitted, however, that if changes in the tonsils are old, the presumption of primary nature of the disease is strong in the absence of marked signs of affection of the lungs or other organs. In this sense only the author wishes to report in this connection a case of apparently primary disease of the tonsil peculiar in that the development of the affection dates distinctly from an exposure to infection. Both tonsils were involved. One tonsil showed a distinct tuberculous ulceration, which is rare, resembling in some respects a chronic diphtheria. Scrapings from the tonsillar ulcer revealed large numbers of tubercle bacilli. The granulations scraped from the tonsil showed tubercle with giant-cell formation. Examination of the extirpated tonsil on the left side showed the same tissue and bacilli. The lymph nodes on both sides of the neck from the angle of the jaw down were much enlarged, and when extirpated and examined showed the presence of cheesy areas, tubercle tissue, and numbers of tubercle bacilli. The nodes showing the oldest infection were high up behind the tonsil.

A. W., male child, aged fifteen months; only child. Father and mother in good health. Patient has hitherto been in good health, with only an occasional bronchitis. Last summer (1902) the parents took the child to Liberty, N. Y. The grandfather was stopping at that place, suffering from pulmonary tuberculosis. The child was with his grandfather quite a good deal and ate at the same table. In the fall of 1902 (November) the child began to suffer from what the physician called tonsillitis. It was at this time in the city. In January, 1903, I saw the patient for the first time. The child was well nourished; slightly rachitic. It had congenital stridor. There was enlargement of both tonsils, especially the left. On this tonsil there was a ragged yellow ulcer, with an appearance resembling a pseudomembranous exudate. There were adenoids. At this time I found no bronchitis, no lung lesion. The cervical lymph nodes at the angle of the jaw were much enlarged. The color of the child was good. There were no enlarged nodes elsewhere. The patient, with ordinary treatment for a tonsillitis, improved. The pseudomembranous appearance of the ulcer on the left tonsil persisted for a time and then cleared up. The nodes at the angle of the jaw continued enlarged. Extirpation of the tonsils and adenoids was advised and carried

out. On cutting the left tonsil it was noticed that there was considerable resistance to the tonsillotome. As the surgeon expressed it, the tonsil had a cartilaginous consistency. After the operation the lymph nodes did not diminish in size—on the contrary. The old ulcer and pseudomembranous coating reappeared on the left tonsil four weeks after the operation. Scrapings taken from the ulcer on the left tonsil showed tubercle bacilli in large numbers, and the tissue scraped from the tonsil showed the structure of tubercle tissue. At this time the general condition of the child had improved and the patient had not lost in weight. The lungs did not show any areas of dulness. On the right side behind, over the lower portion of the lung, there were at times a few coarse râles (bronchitis?). There were at this time no enlarged glands elsewhere in the body; spleen and liver of normal size.

March 10th. Nineteen pounds in weight a month after the operation for adenoids and enlarged tonsils. The child had gained a pound in the past month.

Extirpation of the cervical lymph nodes on both sides and tonsil on left advised and carried out. The extirpated nodes on both sides were much enlarged, the oldest and largest nodes being behind the tonsils on both sides; the affected nodes stretching in a pocket as far as the clavicle.

The enlarged nodes on examination by Dr. C. S. Bernstein, Assistant Pathologist to the Mount Sinai Hospital, were seen to be the seat of tuberculosis. There was typical miliary formation of tubercle tissue, with giant cells and numerous tubercle bacilli in the tissue. The lymph nodes on both sides showed the same pathologic change. Sections of the left tonsil showed tubercle tissue, though no cheesy areas with very abundant tubercle bacilli.

Patient was examined two weeks after operation. The wounds on both sides were fast closing; the left wound had closed by primary union. The child, however, looked as if it had been through a severe operation. The lungs showed no areas of dulness, no bronchitis. There were no enlarged nodes elsewhere.

Two weeks later there was a loss of three pounds in weight as compared to the weight of the child previous to the operation. There was marked dulness over the lower lobe of the right lung behind. From the physical examination, therefore, there would seem to have been an invasion of the lung. The child died three weeks later with signs of tuberculosis of the larynx and lungs.

In the following case there was a packet of tuberculous lymph nodes on the left side of the neck without any accompanying lesion which could be demonstrated clinically. The enlargement of the lymph nodes dates from an affection of the tonsil. At the time of consultation the tonsil on the side of the affected lymph nodes was rather small, with an apparently normal surface. When removed the lymph nodes were found to be cheesy, broken down, containing numerous

tubercle bacilli. The largest nodes were just behind the angle of the jaw, adherent to the sheath of the internal jugular vein. A large number of small red nodes were extirpated, stretching in a chain behind the great vessels of the neck on the left side toward the clavicle. The nodes examined were found to be tuberculous. The tonsil was not examined.

R. G., female child, aged twelve years. Father dead; cause? Mother in good health. Four other children in the family. A child younger than the patient is a delicate child, nine years of age, seen by me in consultation. The diagnosis of lymphatism was made. Child ran a slight temperature, at times one degree above the normal toward evening. The only changes found were very slightly enlarged axillary lymph nodes, inguinal nodes, and cervical nodes. The patient, a sister of the above, had scarlet fever about a year before her visit, followed by an attack of diphtheria. Three months before the visit the mother noticed that the cervical lymph nodes on the left side at the angle of the jaw were enlarged. They have increased in size and are now as large as a walnut. Examination shows this mass to be made up of a number of lymph nodes. There are no enlarged nodes elsewhere. The examination of the lungs shows nothing positive. The percussion over the left apex in front seems slightly higher in pitch, but there are no râles, and there is no change in the voice or breathing. The tonsils are normal in size and appearance. Weight of child, seventy-one pounds. Slightly anemic.

Hemoglobin, 65.7 per cent.; white blood corpuscles, 12,300; red blood corpuscles, 4,088,000; lymphocytes, 34.2 per cent.; large mononuclear, 1.6 per cent.; polynuclear neutrophiles, 63.4 per cent.; mast-cells, 0.8 per cent.

Extirpated packet of a number of enlarged nodes and smaller ones showed that the nodes the seat of advanced cheesy degeneration were high up behind the tonsil, adherent to the internal jugular vein. Adjacent to the vein the nodes were broken down and cheesy; there were a large number of small red nodes stretching toward the clavicle. Histologic examination of the nodes showed tubercle bacilli in the cheesy material. The nodes were the seat of tuberculous changes.

Child now, six months after operation, is in good health.

In this case it seems an inevitable conclusion that the affection and infection of the tonsil were the starting point for the involvement of the lymph nodes.

As a portal of infection there is no reason why the tonsil should not follow the rule and admit of tuberculous infection, as it certainly does of pyogenic or diphtheritic infection. The tonsils, in children especially, are prone to be the seat of repeated inflammatory processes.

During this period of life there is a tendency to the hyperproduction of adenoid tissue. Hypertrophy of the tonsils is very common. The tonsil, from its history during childhood, is anything but inactive. On the other hand, very little is known as to the exact method and avenues by which infection of the tonsil occurs. It is customary for one writer to repeat the other in telling us that the so-called leukocytic migration, which, according to Stoehr, is constantly going on in the follicles, is a potent factor in carrying bacteria from the surface of the tonsil to the interior of its crypts.

As to tuberculous infection, Cohnheim, Orth, and most writers are agreed that the inspired air plays but an insignificant rôle, if any, and that the infection is brought about through the ingestion of infected food (Fuetterungstuberculose). The tubercle bacilli once implanted on the surface of the tonsil, it is still a matter of speculation how these bacteria work their way into the interior of the organ. It is inconceivable how, with a current of leukocytes directed from the interior of the crypts to the external surface of the tonsil (Stoehr), the bacilli gain entrance, granted that there are normal defects in the surface of the mucous membrane covering the tonsil (Hodenpyle and Stoehr). The theory is that the infectious material is drawn into the tonsil by the acts of swallowing. The question has arisen as to whether hypertrophy of the tonsil predisposes to tuberculous infection. It would seem, from the investigations of Pluder, Fischer, Gottstein, Lartigau, Nicoll, and others, that this was so, though tuberculous infection is not as common as we would at first sight suppose, or as some writers contend. Though some authors have found hypertrophied tonsils extirpated *in vivo* to be the seat of tuberculous disease in from 5 to 15 per cent. of the cases, Friedmann has examined a large number of these extirpated organs and failed to find tuberculous disease, even in the above small percentage of cases. We must conclude, therefore, that, on the whole, tuberculous infection of the tonsil of a primary nature is uncommon ; as an isolated infection it is exceedingly rare, for in most cases the lymph nodes communicating with the tonsil are drawn into the picture. There is no doubt also that these nodes become infected from the tonsil in the majority of cases ; that is, from above downward. Of course, in marked tuberculosis of the bronchial nodes and the lungs, the infection of the tonsil may take place against the direction of the lymph current, from

below upward. Most writers contend, however, that this mode of infection is rare. Moreover, in the cases published in which this method of infection was supposed to have occurred, it would be difficult to exclude the infection of the tonsils by the sputum, and thus of the lymph nodes from the tonsil.

The following case, which occurred in my hospital service, appears to me to illustrate the form of tonsillar infection first described by Orth. This child was admitted to my service with all the symptoms of tuberculous meningitis. On admission, also, it was noticed that the lymph nodes on the left side of the neck at the angle of the jaw were enlarged. The tonsil on the same side could only be made out slightly enlarged, but otherwise with no abnormal appearance. After the death of the child the tonsil was extirpated, and, as the report shows, was the seat of tuberculous changes, and contained tubercle bacilli. The enlarged nodes were examined and found to be broken down, cheesy, and the seat of old tuberculous changes ; there were numerous tubercle bacilli. The lungs, as most of the other organs, were only the seat of acute miliary tuberculosis. The above nodes were evidently the oldest seat of tuberculous infection in the body. The bronchial lymph nodes were especially examined to establish the presence of enlargement or old tuberculosis. A reference to the report of the pathologist shows that only one bronchial node was enlarged to the size of a bean, and was not the seat of tuberculous changes. Here we have an evident case of infection through the tonsil of the cervical lymph nodes, resulting ultimately in a general acute miliary tuberculosis.

J. S., male child, aged eight years. Diagnosis, tuberculous meningitis.

Family History. No history of tuberculosis found. Patient is the third of six children, the first two of whom are dead; cause unknown (both less than one year old); other three children healthy.

Previous History. Born at full term. No rash on body, no conjunctivitis. No history of diseases of childhood until three months ago. At that time the child had measles; ill ten days; no cough. After measles complained of pain in neck, and glands below left jaw became considerably swollen; after a month swelling began to subside. No ear discharge; no sore-throat; no cough. Had severe fright about seven weeks ago.

Present History. Child commenced to ail again about six weeks ago, having nothing but a little headache and fever from time to time. About ten days ago the child felt very weak and complained of severe headache; this again disappeared. Since yesterday the child is very stuporous, but recog-

nizes its parents and asks for food. No vomiting. Constipated. No convulsions. Slight cough for past two days.

Status Præsens. General condition poor. Fairly well nourished. Tongue moist and coated. Teeth and gums in good condition. Throat negative. Ears and mastoids negative. Pupils equal, dilated, do not react to light. Eyes move independently, causing various forms of strabismus. Very large glands beneath angle of jaw on left side; smaller ones in supraclavicular space, along anterior border of sternocleidomastoid; no glands elsewhere. Apparently hyperesthetic. Tremor of hands, especially marked on voluntary motion. Rigidity of neck and slight retraction of the head. Kernig moderately marked; no signs of rachitis, but rosary. Babinski present on left foot, marked Macewen. Slight paralysis of left side of face. Hectic flush of cheeks. Tache cérébrale present.

Lungs: anterior. Dulness at left apex and in left axilla; harsh, increased breathing at left apex and in upper part of left axilla. Numerous subcrepitant râles in right axilla.

Posterior. Dulness at left apex, extending to a point half-way between spine and angle of scapula.

Heart. Upper border, third rib; right border, right border of sternum; left border, nipple line; apex beat, diffuse; action, irregular, sounds good, no murmurs; pulse, small, rapid, irregular.

Liver. Fourth rib, dulness; flatness, sixth rib to one finger below free border; palpable at free border.

Spleen. Tympany over splenic area; just palpable.

Abdomen. Lax, tympanitic, somewhat scaphoid, nothing palpable.

Extremities. Patellar reflexes present. No edema. Leukocytes, 15,000.

Lumbar Puncture. 50 c.c. of clear fluids drawn off.

Microscopic Examination. Many small mononuclear leukocytes. Spreads, tubercle bacilli found; cultures, negative; albumin, increased one-eighth inch; sugar, negative; specific gravity, 1004.

March 21st. Child a little more conscious this morning. Paretic symptoms remain the same.

23*d.* Child lies quietly in bed. No convulsions. Internal strabismus of left eye. Respirations irregular; sighing. Heart action irregular. Increase in size of left submaxillary glands.

The temperature in this case ranged from 101° to 102° F. during the week in which the case was under observation. At the close it rose to 104°.

Autopsy. Rigor mortis absent. Poorly nourished. Muscles red. No jaundice. No petechia. No edema.

Thymus: Not enlarged; extending to level of sternal end of clavicles.

Tonsils: Left tonsil considerably enlarged. Right tonsil about normal in size, negative in appearance.

Larynx: On lower border of true cords, about one third the distance from their anterior attachment, are two small, distinct tubercles—one on each cord, not opposite. Rest of larynx negative.

Trachea: Negative.

Esophagus: Negative.

Carotid Nodes: On left side could be distinctly seen and felt. On removal the upper ones were found to be about the size of a walnut, soft, easily broken down, cheesy; spreads showed numerous tubercle bacilli. From above downward the glands gradually became smaller, lost their soft, cheesy character, until, at the clavicle they were hard; on section not degenerated and about the size of a pea. The individual nodes were considerably matted together.

On left side they could neither be seen, felt, nor dissected.

Lungs: Pleural cavities contained no fluid. A few fine adhesions at left apex. Parietal pleura negative. Visceral pleura studded with numerous solitary miliary tubercles on both lungs. Lung parenchyma thickly studded with tubercles. Both lower lobes congested.

Bronchial Nodes: Hardly enlarged, not congested, anthracotic, no cheesy degeneration.

Heart: Pericardium negative. No increase of pericardial fluid. No tubercles.

Heart itself showed some paling of muscle. Mitral valve seat of a recent endocarditis, with fine miliary tubercles on auricular surface of edge. Otherwise flaps negative.

Aorta: Negative.

Coronary Arteries: Negative.

Ductus arteriosus and foramen ovale closed.

Liver: Surface and parenchyma studded with miliary tubercles. Organ normal in size; on section, hard and somewhat congested. Slightly fatty in appearance.

Gall-bladder negative.

Portal vein and ducts negative.

Spleen: Slightly adherent to abdominal parietes. Capsule wrinkled; organ normal in size, hard, not congested, pulp not easily snapped off. Miliary tubercles throughout parenchyma and on surface.

Kidneys: Normal in size, very flabby; capsule not adherent; markings distinct; slight clouding of cortex; otherwise negative.

Adrenals: Negative.

Ureter and Bladder: Negative.

Pancreas: Negative.

Intestines: Beginning at ileocecal valve and extending almost to pylorus were many scattered tuberculous nodules, varying in size from the head of a pin to a small pea. Many of them were degenerated, allowing the expression of a drop of cheesy pus; some were ulcerated on the surface. Peyer's patches not involved. None extended beyond the submucous. Mucous membrane throughout gut somewhat injected.

Colon and Stomach: Negative.

Mesenteric Nodes: Very slightly enlarged; slightly congested; otherwise negative.

Brain: Veins of dura and sinus much congested. Considerable fluid in subarachnoid space. Very little edema at base. Slight adhesions between

duras caput at vortex. Dura and pia mater studded with tubercles. Ventricles (laterals, third and fourth) considerably dilated and filled with clean fluid. Choroid plexus also contained several tubercles, also floor of lateral ventricles; otherwise brain negative.

We have seen that the tonsil is the seat of primary tuberculous infection, though rarely, as compared to the pyogenic forms of infection. The tuberculous tissue is found in the form of giant cells and tuberculous nodules; cheesy degeneration in the tonsil is not common; if the tubercle bacilli are abundant, it is exceptional; tuberculous tonsillar ulcers are rare; as a rule, the lymph nodes leading from the tonsil are affected. Some of these tonsillar infections have been preceded by a simple catarrhal or diphtheritic inflammation of the organ. Tonsillar tuberculosis may be the source of a general tuberculosis of the body. As far as the cervical lymph nodes are concerned, when found the seat of isolated tuberculous infection of a primary nature, it can be justly claimed that such infection has proceeded from the tonsil.

Bibliography.

Stoehr. Virchow's Archiv, 1884, Band xcvii.
Trousseau. Clinique Med., Paris, 1865.
Packard, F. A. American Journal of the Medical Sciences.
Orth. Virchow's Archiv, 1879, Band lxxvi.
Strassmann. Virchow's Archiv, 1884, Band xcvi.
Dmochowski. Ziegler's Beiträge zur Path. Anat., 1891.
Schlenker. Virchow's Archiv, Band cxxxiv.
Krueckmann. Ibid., Band cxxxviii.
Ruge. Ibid., Band cxliv.
Gottstein. Berlin. klin. Wochenschrift, 1896, p. 31.
Busse. Virchow's Archiv, 1896.
Friedmann. Ziegler's Beiträge, 1900.
Schlessinger. Berliner Klinik, 1896.
Scheibner. Deutsche med. Wochenbl., 1899, p. 343.
Pluder and Fischer. Archiv f. Laryngologie u. Rhinol., 1896.
Fraenkel, E. Zeitschr. f. Ohrenheilk., Band x.
Brindel. Gaz. hebdom d. Laryngol., Bordeaux, 1896.
Trautmann. Anat. und Path. Studien über Hyperplasie der Rachentonsillen, Berlin, 1886.
Oppenheimer, S. Medical News, 1898.
Lartigau and Nicoll. American Journal of the Medical Sciences, 1902.

A CASE OF EXTREME MALFORMATION OF THE HEART.

By JAMES HOMER WRIGHT, M.D.,
OF BOSTON,

AND

ARTHUR K. DRAKE, M.D.,
OF TEWKSBURY, MASS.

The following case of malformation of the heart is considered to be worthy of record, because of the extreme degree of the malformation and because of the unusual number of nucleated red corpuscles which were found in the blood during some weeks immediately after birth:

George C., born at the State Hospital, Tewksbury, Mass., February 11, 1900. At birth he was well developed and nourished, weighing nine pounds. A moderate degree of general cyanosis was evident, which became greatly exaggerated while crying.

On the following day attention was called to the heart on account of the persistent cyanosis. Area of cardiac dulness was to right of sternum, apex beat in fifth interspace just below the right nipple. No murmurs were present. Liver in normal position and no apparent transposition of the other viscera. Up to the age of nine months the cyanosis gradually lessened and the child seemed to be in perfect health, weighing eighteen pounds, when he began to have sudden attacks of collapse, accompanied by extreme cyanosis, rapid pulse, feeble heart sounds and rapid respirations. The child rallied from these attacks until December 15, 1900, when he died at the age of ten months and fourteen days.

The blood examinations are of considerable interest because of the remarkable persistence of very many nucleated red corpuscles. At the age of two weeks, when the first examination was made, the number of normoblasts and megaloblasts combined outnumbered the white cells two to one. It was impossible to obtain an exact white count, as the acetic acid brought out the nuclei of the red cells as well as of the leukocytes.

The following are the results of examinations of the blood:

Two weeks of age: Polynuclear leukocytes, 38 per cent.; small lympho-

FIG. 1.

Showing the heart and the single large aorta-like vessel with its principal branches.

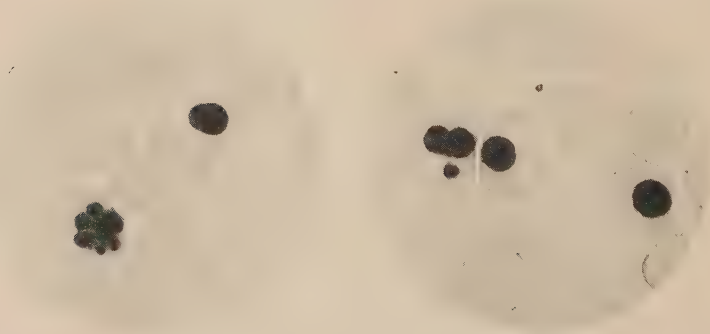
FIG. 2.

Showing the ventricle and aorta-like valve opened. The supposed rudimentary ventricular septum, the valve of the aorta-like vessel, and the large branching vessel given off from the aorta-like arch are shown.

FIG. 3.

The auricle and ventricle are opened to show the rudiment of the auricular septum and the single auriculoventricular valve.

FIG. 4.



Photomicrographs of the blood of the patient, indicating the large number of nucleated red cells.

These figures are from photographs by Mr. L. S. Brown, Clinico-Pathological Laboratory, Massachusetts General Hospital.

cytes, 45 per cent.; large lymphocytes, 13 per cent.; eosinophiles, 2.5 per cent.; transitional forms, 1 per cent.; myelocytes, 0.5 per cent.; normoblasts 1156, seen while counting 500 white cells; megaloblasts, 45, seen while counting 500 white cells; red corpuscles, 6,000,000; hemoglobin, 100 per cent.; estimate of white cells, 12,000.

Four weeks of age: Polynuclear leukocytes, 58 per cent.; small lymphocytes, 34 per cent.; large lymphocytes, 7 per cent.; eosinophiles, 0.8 per cent.; transitional forms, 0.2 per cent.; normoblasts, 115, seen while counting 1000 white cells.

Eight weeks of age: Polynuclear leukocytes, 30 per cent.; small lymphocytes, 50 per cent.; large lymphocytes, 18 per cent.; eosinophiles, 0.8 per cent.; transitional forms 1.8 per cent.; no normoblasts found.

Eight months of age: Polynuclear leukocytes, 17.6 per cent.; small lymphocytes, 55.8 per cent.; large lymphocytes, 25.4 per cent.; eosinophiles, 0.8 per cent.; transitional forms, 0.4 per cent.; normoblasts, 6, seen while counting 500 white cells.

At the autopsy the heart was found lying chiefly in the right side of the thorax. There was no transposition of the principal viscera.

The heart with the aorta in continuity, together with only the proximal portions of the vessels springing from the latter, are available for description.

The heart is probably slightly larger than is normal for an individual of the age of this one. The auricular and ventricular portions are well defined externally. From the anterior and superior portions of the ventricle there arises a single large vessel, which appears to represent both the ascending aorta and the pulmonary artery and curves backward after the manner of the arch of the aorta to become continuous with the descending aorta. From the superior portion of what seems to represent the arch of the aorta and at a point about 3.5 cm. from the ventricles, there is given off a large vessel which quickly divides into two trunks of unequal size. Immediately beyond this there are given off two other good-sized vessels from the convexity of the arch. The general appearances and relations of the vessels are shown in the photographs (Figs. 1 and 2). From the concavity of the arch, opposite the large vessel of the convexity situated farthest from the ventricle, the stump of a small artery less than 2 mm. in internal diameter is present. This is not shown in the photograph.

As it is impossible to determine the distribution of these vessels given off by this aorta-like trunk, it is useless to speculate as to their homologies.

The large trunk given off from the ventricle is without any septum or indication of such. At its origin from the ventricle it presents three semilunar valves, each provided with a sinus of Valsalva. From each of the two posterior sinuses a coronary artery originates. The ventricular portion of the heart upon being opened is seen to have a single cavity. A ridge-like thickening, however, springing from the anterior wall would seem to be a rudiment of a ventricular septum. This is well shown in Fig. 2. The general appearances of the ventricular cavity are illustrated in this figure and in Fig 3.

The auricular portion of the heart has two appendices and consists essentially of but one cavity traversed by what seems to be the rudiment of an auricular septum in the form of a fan-shaped band with a cord-like branch as is shown in Fig. 3. The broader portion of this band is attached to the posterior wall of the auricle, while the narrower portion is attached to the anterior wall of the auricle, as shown in the photograph. This rudiment of septum divides the auricle into two unequal portions, of which the left is much smaller than the right. It probably represents the so-called "septum primum" or "septum superius" of the embryonic auricle.

The auricular and ventricular cavities communicate with one another by a single valve, which seems to be more bicuspied than tricuspid in form. The rudimentary auricular septum has no connection with this valve.

In brief, this heart is regarded as an example of a heart arrested in its metamorphosis at an early period of embryonic life. It is an instance of persistence of the primitive truncus arteriosus, of only rudimentary development of the ventricular and auricular septa, and of a single auricular ventricular valve.

THE ADRENAL GLAND AND ITS ACTIVE PRINCIPLE IN THEIR RELATIONS TO CYTOLYSINS AND ANTITOXIN PRODUCTION.

By A. C. ABBOTT, M.D.,
PROFESSOR OF HYGIENE AND BACTERIOLOGY, AND DIRECTOR OF THE LABORATORY OF HYGIENE, UNIVERSITY OF PENNSYLVANIA.

(From the Laboratory of Hygiene, University of Pennsylvania.)

I. Introduction. In the course of an investigation upon the relation of certain bacterial toxins to particular organs of the body, the details of which need not concern us at this time, it became desirable to experiment upon guinea-pigs from which the adrenal bodies had been, in part or wholly, removed or in some other manner rendered physiologically inactive.

Our efforts to meet this requirement have led us far from the original object of the research, but at the same time have supplied information that we regard as of sufficient general interest and importance to justify its embodiment in a special communication.

As is well known, removal of the adrenal bodies from guinea-pigs by the customary surgical procedure is almost invariably fatal within a few hours. Our own experience in this field was in nowise different from that of other investigators.

Destruction of the glands by the direct injection of corrosive substances—such, for instance, as strong iron chlorid solutions—was in our hands likewise fatal within from six to ten hours, so that both of the foregoing procedures were abandoned as umpromising after a few trials.

At the time these experiments were begun[1] the state of our knowledge upon the reactions in the animal body resulting from the intro-

[1] Spring of 1902.

duction of alien cells, fluids, and tissues led us to hope that the treatment of animals with the fresh adrenal cells of the guinea-pigs would ultimately result in the appearance in the blood of the treated animal of substances having a specific, probably specifically destructive, relation to the guinea-pigs' adrenals *in situ;* and that by the use of such specific cytolytic sera upon guinea-pigs the partial or complete elimination of their adrenal glands might be accomplished, and this, too, in so gradual a manner as not to endanger the life of the animal to the same degree as is usual with the surgical procedures. We were encouraged in this hope not only by the ingenious doctrine applying to the artificial induction of cytolysins in general, but more particularly by the investigations of Bigart and Bernard[1] that had a direct bearing upon the problem before us. These investigators state that after the intraperitoneal injection of ducks with guinea-pigs' adrenals the sera of the ducks, when injected into the peritoneal cavity of the guinea-pig, manifest a specific affinity for the adrenal glands. This is evidenced by a swelling of the adrenals without alteration of shape, and by more or less complete discoloration and gelatiniform softening of the medullary portion of the glands. The authors state that the microscopic alterations of the gland are profound, but reserve the detailed description for a subsequent publication.

As we have not encountered their later communication, it is scarcely possible from the foregoing description to form an adequate conception of either the local or general conditions produced in the animals upon which they operated.

II. Method of Immunization. In the studies to be here recorded an effort was made to secure a specific cytolytic serum for the adrenals of the guinea-pig by the repeated intraperitoneal injection of rabbits with freshly-prepared infusions of guinea-pigs' adrenals. The glands were removed from normal animals, of as large size as could be secured, were carefully freed from all adherent blood by washing in 0.85 per cent. sodium chloride solution, were then rubbed up in a porcelain mortar with the same solution, and, after straining through cheese-cloth, were injected directly into the peritoneal cavity of the rabbit by means of a hypodermic syringe, strict aseptic precautions having been observed throughout. No deaths resulted from

[1] Compt. rend. heb.Jd. l. Soc. d. Biol., 1901, p. 161.

infection after such injections, and we were surprised to find that the effects in general upon the rabbit were, as a rule, inconsiderable, there being neither evident discomfort, disturbance of circulation nor respiration, nor either elevation or depression of rectal temperature. The number of adrenals injected at one time, as well as the interval between the injections, varied. The maximum number of glands used for a single injection was six, and the intervals between the injections were from three to ten days. In all, five rabbits were employed.

Rabbit A received 23 guinea-pig adrenals between September 8 and December 5, 1902; Rabbit B, 31 adrenals between September 8, 1902, and January 23, 1903. Rabbit C died after the second injection of two adrenals, with nothing to account for death. Rabbit D received 32 adrenal glands between December 16, 1902, and February 26, 1903, and Rabbit E received 38 adrenals between December 26, 1902, and March 19, 1903.

In all the rabbits treated in this manner there was a progressive loss of weight, reaching, ultimately, between two hundred and fifty and three hundred grams. The weight of one of the animals (Rabbit E) fell from 1960 grams at the beginning of the immunization (on December 26, 1902) to 1200 grams on March 19, 1903. This fact renders it somewhat doubtful if we could have kept our animals alive had larger numbers of the glands been employed for the injections. Two of the rabbits were bled and the action of their serum tested after they had received seventeen adrenals each, one after fourteenth and a fourth after thirty-eight. One of the five original rabbits (Rabbit C) died so early in the course of immunization that it was discarded.

The method of bleeding employed is that of Latapie,[1] which, for neatness, dispatch, and general satisfaction, is so far superior to any other means tried by us that we have abandoned all other procedures for it.

III. Effect of the Immune Serum on Guinea-pigs. The most striking effect upon guinea-pigs of intraperitoneal injection of serum obtained from rabbits after this plan of treatment is seen within a few minutes of injection. In five minutes, more or less, after a dose of from one-half to one cubic centimeter, according to the activity of the serum, the pig may settle upon its belly or its side,

[1] Annales de l'Institut Pasteur, 1900, Tome xiv. p. 106.

with legs alternately flexed and extended. It may be unable to stand, and, if placed upon its feet, falls almost at once into the prone posture. Occasionally the immediate effects are less marked, though some degree of depression is invariably observed. Its rectal temperature is often quickly reduced, reaching, after another fifteen or twenty minutes, one and one-half and even two degrees below normal. At times these acute symptoms disappear within one or two hours, and the animal may go on to recovery; again the conditions may become progressively worse and death supervene in a few hours. Almost immediately following the injection there is profuse urination, and in from seven to ten hours the urine may be blood-stained, though this is not invariably the case. Movements of the bowels commonly follow the injection; at times they are more moist than is common to the guinea-pig. We have not seen them to be blood-stained.

In animals that succumb within twelve to twenty-four hours there is often to be observed varying degrees of subcutaneous œdema; constantly an enlargement and often congestion of the subcutaneous lymphatics; a yellowish discoloration of the subcutaneous fat; at times blood-stained serum in the serous cavities; a purplish tinge to the muscles and membranes; enlargement and injection of the retro-peritoneal lymph glands, and a swollen, soft, and almost black condition of the spleen, this organ being frequently very much enlarged.

In animals that have died within a few hours after the injection the liver is often congested. If death be postponed the organ may be marked by irregular, bright red areas, paler than the surrounding parts of the organ. These are seen not only upon the surface, but may extend well into the substance of the liver. Where death is still more delayed the liver may be, in general, of a distinct yellow or ochre color. Both the gall-bladder and the urinary bladder are frequently distended with highly-colored contents, the latter containing usually more or less of blood. The cortical portions of the kidneys, especially of animals that die, roughly, in about three days after the injection, are often (not always) of a dark chocolate color, while the pyramids are stained of a dirty slate color. The lungs may be normal, may be uniformly congested, or may present irregular, tiny areas of consolidation, having the appearance of thrombotic areas.

The blood is frequently conspicuous for its peculiar "thin" ap-

pearance, being often so poor in normal coloring-matter as to be almost transparent when viewed by transmitted light through such diaphanous tissues as the omentum or mesentery. The clots in the heart are paler than usual, and have more of a transparent, ruby color than that of the dark, opaque masses peculiar to normal blood seen after death in this situation. Tested by the Talquist process the shade given for such blood is often (not always) scarcely more than that indicated on the scale by a hemoglobin content of ten per cent.

EXHIBIT I.—EXPERIMENT OF JANUARY 4, 1903.

Intraperitoneal injection of guinea-pigs with "adrenal serum" from Rabbit B.

Pig.	Weight.	Dose of untreated serum.	Dose of serum heated to 55–56°C. for 30 min.	Dose of heated serum and fresh infusion of adrenals.[1]	Rectal temp. within one hour after injection.	Results.
14	490	1.5 c.c.	.....	.....	34.6° C.	Dead in 3½ days. Blood thin; liver pale yellow; fat yellow; kidneys dark chocolate color; irregular areas of consolidation in lungs; adrenals not certainly affected; spleen a little swollen; hemoglobinuria.
15	430	1.5 c.c.	.....	.....	34.0° C.	Dead in 5 hours. Vessels of mesentery and omentum injected; kidneys and adrenals very much congested; areas of consolidation in lungs; serous tissues and muscles of a diffuse purple color.
16	380	.....	2 c.c.	.....	35.8° C.	Dead in 3½ days. Counterpart of Pig 14, except that the spleen was more involved.
17	370	.....	2 c.c.	.....	33.2° C.	Dead in something less than 3 days. Blood thin; liver ochre color; fat yellow; bile dark brown; hemoglobinuria; kidneys dark chocolate color; spleen only moderately swollen and darkened; adrenals not perceptibly altered.
20	440	.....	.....	4 c.c.	38.3° C.	Dead in 92 hours. Yellow fat; pale yellow liver; chocolate-colored kidneys; consolidated areas in lungs; blood in urine; blood thin and watery; adrenals not certainly affected, did not differ from those of foregoing animals.
21	460	.....	.....	4 c.c.	40.0° C.	Dead in less than 17 hours. Consolidated areas in lungs; adrenals a little darker in color than usual; mesentery and omentum injected; liver and spleen normal; tissues in general of a purplish color; intestines contained a few c.c. of dark brown mucoid fluid; kidneys congested; small quantity of blood-stained serum in both pleural cavities.

[1] For this test two freshly removed guinea-pig adrenals were rubbed up in the mortar with 5 c.c. of sterile 0.85 NaCl solution. This was mixed in equal parts, after straining through gauze, with the serum and 4 c.c. of the mixture used for injection after it had stood at 38° C. for thirty minutes. By this plan the actual dose of serum for each animal was 2 c.c., as in animals 16 and 17.

The adrenals may be normal, congested, or darkened in color, according to the time that has elapsed between the injection and the death of the animal. They are not enlarged, and, on section, show nothing that suggests to the naked eye a disturbance of the normal condition, relations, or proportions of the zones composing them.

In brief, the entire picture suggests a rapidly-acting, blood-destroying process, an impression that is borne out by microscopic study of the organs.

In marked cases microscopic examination of the blood reveals the presence of erythrocytes in all stages of disintegration and distortion. Many of them appear fused together into soft, tenacious masses that, by the pressure of the coverslip, are pressed out into long, adherent, "sticky" bands or irregularly-outlined masses. While many normal erythrocytes are to be seen, there are also many that are irregular in size and form and many that are much paler than usual.

Microscopic examination of the liver shows the capillaries of the irregular, bright red areas, mentioned above, to be conspicuously filled with blood and to be surrounded by liver cells in varying stages of degeneration. Little or nothing of nuclear fragmentation is to be observed, and the change noted gives the impression of being due more to circulatory disturbance than to the action of specific intoxicants upon the tissues. It is possible that these lesions may result from the occurrence of agglutinative thrombi, though on this point we hesitate to speak with certainty. In the advanced cases, where the liver presents the uniform yellow color mentioned, it is found on microscopic examination to be in a condition of diffuse, fatty degeneration, with occasionally here and there islands having somewhat the appearance of hyaline change.

The spleen is usually markedly congested, and is often conspicuous for the presence of large phagocytic cells, many of which are filled almost to bursting with erythrocytes in various stages of deterioration. Often the sections are marked by the presence of large, round, or oval bronze-colored masses, evidently representing blood-coloring matter. No definite crystal forms were observed. In two or three cases the cells of the lymph nodes of the spleen gave evidence of destructive changes, many of the nuclei being distorted and fragmented.

The kidneys frequently present a most striking picture. They are

markedly congested. There is often to be observed ruptures of the glomerular capillaries, with escape of blood into the capsule; and the epithelium of both the convoluted and the looped tubules is conspicuously marked by the presence of closely-packed tiny round or oval brownish granules, evidently the débris of destroyed erythrocytes.

On section the adrenals are usually found congested, though this varies. Rarely there are tiny points of hemorrhage; but definite necrosis or degeneration has not been detected in any of our animals. Early in the work we were encouraged by discovering evidence of cell multiplication in these organs, but subsequent study, not only of additional cases in this group, but of the adrenals from normal guinea-pigs, as well as from those dead of other causes, lead us to believe that nuclear division may be commonly observed in the cells of this organ in health as well as in disease. It may be of interest to note that whenever karyokinesis was observed it was most pronounced in "zona fasciculata" near its junction with "zona glomerulosa."

By microscopic as well as macroscopic examination we have found no regular difference, save for the varying degrees of congestion and slight alterations in color, between the adrenals of these and those from normal animals, or from animals dead after other modes of treatment.

The foregoing composite picture, drawn from a number of animals treated with serum from rabbits that had received injections of guinea-pigs' adrenals, so forcibly suggests blood-destruction as the underlying cause of death and the conditions found that a series of control experiments, designed to acquaint us with the changes resulting from the injection of actively hemolytic sera, were instituted. For this purpose guinea-pigs were injected with sera as follows: In the one group with sera from rabbits rendered highly immune from guinea-pigs' erythrocytes; in the other with the serum of normal rabbits, which, as is known, possesses more or less hemolyzing power for guinea-pigs' erythrocytes, at least *in vitro*.

The results of intraperitoneal injection of guinea-pigs with normal rabbit serum may be dismissed in a few words. While rabbit serum is hemolytic (in varying degrees) for guinea-pigs' erythrocytes in the test tube, it is not necessarily destructive to life when injected into

the living animal, and may often be used in large doses with no effect whatever, though this is not invariably the case. For instance: Two of our animals (Pigs 95 and 96—the one weighing 260, the other 270 grams) received intraperitoneal injections of such relatively large doses as five and one-half cubic centimeters each of normal rabbit serum without more than temporary inconvenience that passed off in about an hour, and from which the animals ultimately recovered; while others (Pigs 3 and 4, weighing, respectively, 210 and 190 grams) succumbed to the intraperitoneal injection of three and three and one-half cubic centimeters, respectively, of normal rabbit serum, both dying in seven days after the injection, neither presenting positive evidence of a destructive action of the serum upon the blood or organs, and the peritoneal cavity of both being sterile by culture tests. From the variations in the hemolytic activity of serum from different normal rabbits as exhibited upon guinea-pigs' erythrocytes *in vitro*, it is reasonable to expect variations in other properties as well, and the foregoing discrepancy may be, in part, at least, explained in this way. The hemolytic activity of one of the sera mentioned above (that used in the large doses) was determined *in vitro*, and was found to be conspiculously low as compared with the average for rabbit serum upon the red corpuscles of the guinea-pig.

EXHIBIT II.

Pig.	Weight.	Dose.	Rectal temperature 15 min. after injection.	Results.
24	310	0.5 c.c.	35° C.	Dead in less than three days. Hemoglobinuria during last day.
25	329	1.0 c.c.	36.9° C.	Dead in twenty-four hours. Hemoglobinuria.
26	340	1.5 c.c.	35.8° C.	Dead in less than two days. Hemoglobinuria.
27	390	2.0 c.c.	35.1° C.	Dead in less than two days. Hemoglobinuria.
Control	.....	.....	38° C.	

With the serum from rabbits rendered highly immune from guinea-pigs' erythrocytes, on the other hand, the results were quite different. These sera, when highly hemolytic—*i. e.*, when from highly-immunized animals—are almost invariably quickly fatal to guinea-pigs by intraperitoneal injection, even in comparatively small doses.

Thus, for instance, the following results of intraperitoneal injection of guinea-pigs with specific hemolytic serum were observed. The serum used was from a rabbit that had received by intraperitoneal injection seventy-five cubic centimeters of defibrinated guinea-pigs' blood in broken doses.

The symptoms exhibited by these animals immediately after the injection are identical, save in degree, to those noted in the animals that had received the adrenal serum,[1] and the conditions found post-mortem are likewise not essentially different. Beyond the fact that the lesions are more marked, there is the same involvement of lymphatics, the same irregular markings and more pronounced degenerations (according to the date of death) of the liver, the large, soft, almost black, spleen, the frequent brown discoloration of the kidneys, the widespread evidence of blood destruction, with hemoglobin staining of the tissues, and the same indefinite effect upon the adrenal glands that were noted in the animals dead after injection with the "adrenal serum." In animals that survive for a longer time than those cited above, some one or another of these features may be modified, but it is the rule to find recent or remote evidence of blood destruction, degeneration of the liver, alterations in the spleen, and either discoloration or congestion of the adrenal bodies. In the animals that die within forty-eight hours of the injection, the gall-bladder and urinary bladder are usually distended with dark fluids, in the latter case evidently blood-stained. In animals that survive for several days these conditions may be less conspicuous, or even absent. Hemoglobinuria within twenty-four hours of the injection is, practically, always seen, especially if an actively hemolytic serum be used. From our observations the conditions of guinea-pigs after injection with an actively "hemolytic serum" do not differ except in being more pronounced from that following injection with "adrenal serum," and it is furthermore usually impossible to distinguish, by either macroscopic or microscopic examinations, between the tissues from the two groups of animals.

IV. Effects Produced by Modified Serum. When it became obvious that a conspicuous property of the "adrenal serum"

[1] For the sake of brevity, the expression "adrenal serum" will be used for the serum of rabbits that had received intraperitoneal injections of fresh emulsions of guinea-pigs' adrenals; and the term "hemolytic serum" for that of rabbits immunized from guinea-pigs' erythrocytes.

is a marked degree of hemolyzing power, it seemed possible for our failure to secure evidence of specific action of this serum upon the adrenal glands *in situ* to have been due to the death of the animals from destruction of blood before the specific effects of the serum upon the adrenals was made manifest.

With this in view an effort was made to separate from the adrenal serum its hemolytic receptors. To this end adrenal serum, heated to 55–56° C. for thirty minutes to destroy complement, was mixed with an equal volume of washed guinea-pigs' erythrocytes placed in the incubator for two hours, and, in some cases, used for injection at once; in others, left at ice-chest temperature overnight. There was always a marked agglutination of the red corpuscles, so that their separation from the fluid portion of the mixture was a matter of no difficulty. An "adrenal serum" so treated, when injected into guinea-pigs in amounts equivalent to the fatal dose of untreated serum, was without effect, either immediate or remote.

By heating the adrenal serum (to 55–56°C.) for thirty minutes its acute effects noted above are not necessarily modified. The receptors in the serum find, therefore, their appropriate complement in the body of the guinea-pig. By mixing together heated "adrenal serum" with a fresh infusion of guinea-pigs' adrenals in 0.85 per cent. sodium chloride solution its fatal hemolytic effects upon the guinea-pig are not necessarily eliminated, death often resulting from destruction of blood, just as was seen to follow the use of the unheated serum. (See Pigs 20 and 21, Exhibit I.)

As stated above the immediate effects of the untreated serum, either the "adrenal serum" or the specific "hemolytic" serum, are marked, being manifested by extreme prostration with coincident depression of rectal temperature. By mixing such sera with either washed guinea-pigs' erythrocytes or with fresh infusions of guinea-pigs' adrenals in 0.85 per cent. sodium chloride solution,[1] as outlined above, the immediate effects of the sera are, as a rule, caused to disappear, the animals showing, practically, no depression of temperature or irritation after the injection.

[1] In the mixtures we have used washed guinea-pigs' erythrocytes in equal volume with the serum. Where adrenal infusions were employed, two glands were usually rubbed up with eight to ten cubic centimeters of 0.85 per cent. NaCl solution, and this added to the serum in equal parts. The necessary corrections for these dilutions were made in adjusting the dose of serum.

V. Reactions of the Serum in Vitro. These results, though disappointing in so far as our desires were concerned, are not devoid of interest, and gain in this respect through the fact that the test tube reactions of the several sera employed were, with one exception (adrenal serum from Rabbit E), just as one would have anticipated. The untreated adrenal serum was actively hemolytic for guinea-pigs' erythrocytes and actively agglutinative for fresh infusions of adrenal glands.

By heating (to 55° C.) for thirty minutes the hemolyzing action was checked, if carefully-washed guinea-pigs' erythrocytes were employed; but there was always some agglutination to be seen, and the agglutinative action of the serum upon the adrenal cells was unaltered.

We endeavored to detect a lytic effect of the "adrenal serum" upon the adrenal cells in the test tube, but with little or no success. Agglutination was with one exception always observable, and appeared at times within a few minutes after the mixture of serum and infusion was made.

Similar tests with the specific "hemolytic" serum of rabbits treated with guinea-pigs' blood gave in the test tube hemolysis or agglutination of washed guinea-pigs' erythrocytes, according to the manner of testing; but never the least effect upon the adrenal gland infusions.

The "adrenal serum" from one of the rabbits in the group offered a confusing exception to practically everything that has been said above. This animal (Rabbit E) received thirty-eight guinea-pigs' adrenals (between December 26, 1902, and March 19, 1903). Six days after the last injection of six adrenals, ground up in twelve cubic centimeters of 0.85 per cent. sodium chloride solution, it was bled for the first and only time. Its untreated serum in gradually ascending doses (from 0.5 c.c. to 2.5 c.c., inclusive) had nothing more than a temporarily depressing effect (tolerably marked in the larger doses) upon guinea-pigs of from two hundred and thirty to two hundred and seventy grams weight. The serum, after heating (to 55°–56° C.) for thirty minutes, had no immediate effect upon guinea-pigs of two hundred to two hundred and twenty grams' weight when given in doses of one and one-half and two cubic centimeters, respectively, intraperitoneally. One of these pigs died after five days, with nothing to

account for death. There had been no hemoglobinuria, and the autopsy revealed no evidence of blood destruction or of involvement of the viscera. When the serum was heated and left in contact with washed guinea-pigs' erythrocytes (two parts of serum to one of erythrocytes), by the customary plan for the removal of hemolytic receptors, it had no immediate effect upon four guinea-pigs of from two hundred and ten to three hundred and thirty grams in weight when administered intraperitoneally in doses of 2.5 c.c., 2.5 c.c., 3 c.c., and 4.5 c.c., respectively. One of the four pigs (No. 129) died in two days after intraperitoneal injection of 2.5 c.c. of the serum. There was no evidence of blood destruction, and careful inspection showed the organs to be normal.

As compared with the serum of a normal rabbit, selected at random, the hemolytic activity of this serum upon washed guinea-pigs' erythrocytes in the test tube was from four to five times as great—that is to say, 0.01 c.c. of the "adrenal serum" brought about the same degree of hemolysis in the standard suspension of washed guinea-pigs' erythrocytes—as was caused by 0.04 to 0.05 c.c. of the normal serum.

After heating, its hemolyzing action naturally disappeared, though it was still actively agglutinative for the red corpuscles of the guinea-pig.

But in neither the unheated nor the heated condition had it the slightest effect upon a fresh infusion of guinea-pigs' adrenals when mixed in the proportions of 0.05 c.c. and 0.1 c.c. of the serum to 2 c.c. of an infusion of two glands in 15 c.c. of 0.85 per cent. NaCl solution.

We have no satisfactory explanation for this anomaly. The rabbit had lost weight, it is true, but was otherwise free from disease at the time it was killed—*i. e.*, immediately after it was bled. An interval of six days had elapsed between the date of the last injection of adrenal infusion and the time of bleeding. This may have been too brief. It is possible that we have here an individual exception to the general rule. This is not unknown in experiments of this character.

VI. Definite Results. Concerning the condition of the adrenal bodies after the injection of these two types of sera into guinea-pigs, it is important to note that specific degenerative or necrotic lesions, reasonably referable to the action of the sera, were encoun-

tered on but two occasions, and, singular to say, these were among the animals that had received the "hemolytic" rather than the "adrenal serum." In one animal (Pig. 92), dead after an injection of "adrenal serum" that had stood in contact with a fresh infusion of guinea-pigs' adrenals by the customary method, both adrenal bodies were found markedly enlarged, and in both karyokinesis was so much in evidence throughout the cells of zona fasciculata as to leave little doubt of its relation to the treatment to which the animal had been subjected, though, as said above, nuclear division in varying degrees is so commonly observed in these glands as to render its significance in this particular case more or less doubtful; moreover, the contact of the serum and the fresh infusion of the gland in the test tube before the injection should, theoretically at least, have robbed the serum of those principles having specific affinities for the cells of the gland *in situ*.

The protocols of the pigs in which the adrenal bodies were definitely affected (Pigs 89 and 94, experiment of January 24th with "adrenal serum" and "hemolytic serum") are, briefly, as follows:

Pig 89, 250 grams in weight, received an intraperitoneal injection of 1.25 c.c. of "hemolytic" serum that, after heating to 55–56° C. for thirty minutes, had stood in contact with an equal value of washed erythrocytes of the guinea-pig (two hours at 37–38° C. and overnight in the ice-chest). Theoretically the hemolytic receptors should have been removed. It died about ninety-six hours after the injection. Hemoglobin was not certainly present in its urine at any time, though the urine was highly colored. At autopsy the subcutaneous fat was yellowish in color; lymphatics enlarged, though not hemorrhagic or congested; peritoneum normal, though the fat was of a yellowish tinge; the liver was of a uniform yellow or ochre color; gall-bladder distended with dark-colored bile; intestines normal; spleen dark in color and only moderately enlarged; both kidneys pale; left adrenal of a yellowish color, and there was a tiny subscapular hemorrhage toward its posterior extremity; right adrenal ditto, except for the superficial hemorrhage; lungs normal; myocardium and its lining membrane, especially the latter, somewhat hemoglobin stained; blood "thin," and generally "watery" in appearance; clots in the heart less dark in color than normal; highly-colored urine in the bladder.

Culture tubes inoculated from the peritoneal cavity remained sterile.

Microscopic Study. Zona fasciculata in both adrenal bodies marked by areas of irregular size and outline, in which there was more or less destruction of tissue. There was conspicuous invasion of these areas by leukocytes, many of which contained eosinophilic elements, and at a number of points

there was evidence of fragmentation of the nuclei of the fixed cells. The capillaries traversing these areas were conspicuously filled with blood, and at points were marked by large numbers of polymorphonuclear leukocytes packed within them. Many of the eosinophilic cells observed in these sections—and they were numerous—were much smaller than usual, were not distinctly granular, as one commonly sees them, and gave the impression of being undeveloped "eosinophiles." Throughout the organs were a number of isolated areas, in which the capillaries were very much engorged with blood, at times almost to the point of bursting without there being at the same time any discernible necrosis or degeneration of the immediately surrounding tissues. The points at which necrosis was beginning were marked by a conspicuous accumulation of polymorphonuclear leukocytes.

There is no evidence of proliferation of the fixed cells of the organ other than an occasional karyokinetic figure. Beyond congestion the medullary portion of the organ was unchanged. It is reasonable to refer these degenerated areas to the development of agglutinative thrombi in the vessels supplying them, though the treatment to which the serum had been subjected before it was used aimed to remove this principle. In a number of our tests *in vitro*, however, we found that not all of the agglutinative principle in a specific hemolytic serum is necessarily removed by such an arbitrary combination as serum and erythrocytes in equal volumes, these being the proportions used in this experiment.

The liver was marked by widespread fatty degeneration, varying in extent in different portions of the organ. There were no circumscribed areas of necrosis and no evidence of nuclear fragmentation.

The kidneys did not present the condition of pigmentation so often seen in these organs after injection with a hemolytic serum, nor can it be certainly said that rupture of the glomerular capillaries was observed, though at a few points tiny areas suggested this accident.

Pig 94, 370 grams in weight, died in about seventy-two hours after intraperitoneal injection of 1 c.c. of a "hemolytic serum," which, after heating for thirty minutes to 55°–56° C., had stood in contact with a fresh infusion of guinea-pigs' adrenals in 0.85 per cent. NaCl solution. By this preliminary treatment the principles, if any there were, having affinities for the adrenal tissues *in situ*, should have been removed from the serum.

In general, the conditions found at autopsy in this animal corresponded with those observed in Pig 89, just described. They differed, however, in that there was more conspicuous evidence of blood destruction, in that the kidneys were involved, being of a dark chocolate color, congested, and markedly pigmented, as revealed by microscopic study, and in that the adrenal bodies presented several areas, giving somewhat the reactions of hyaline tissue, though not fully characteristic. No destruction of nuclei was observed in these areas, and, in general, nuclear staining differed little from normal. The cell protoplasm took up eosin more conspicuously than usual, and more so than the surrounding portions of the sections, and had

the appearance of being fused together, so that the outlines of individual cells were difficult, and, at times, impossible, to detect. A similar condition was seen in zona reticulosa. In this locality it was not isolated, as in zona fasciculata, but was more generally diffused. While no fragmentation of nuclei was seen, still many of the nuclei were conspicuous for the unusual distribution of their chromatin. In this zone were numerous apparently degenerated and unusually vacuolated cells. The condition found in the adrenals of this animal was by no means so definite as in the preceding pig, and was manifestly of different origin. The peritoneal cavity of this animal was found to be sterile by culture tests. In both autopsies there was evidence of blood destruction in varying degrees.

VII. General Comments. If it be insisted that the serum of animals immunized by the injection of definite types of alien cells shall have a specific affinity for only those cells—that is to say, shall be possessed of only specific morphologic affinities—then obviously the results here recorded are at variance with the doctrine governing our conceptions of artificially induced cytolytic sera in general. If, on the other hand, it be admitted that the specificity of these sera is chemical in its relations, then there can be no reasonable grounds for surprise that such sera occasionally manifest affinities not only for the cells with which the animal furnishing the serum had been treated, but for other elements of the body as well, for it is scarcely justifiable to assume that morphologic distinction means necessarily chemical distinction throughout. In many particulars the different cells of the body, even though morphologically and physiologically unlike, possess, nevertheless, certain chemical constituents in common, and it seems not unlikely that the multiple activity or the apparent lack of strict specificity occasionally exhibited by certain of the cytolytic sera may be referable to the stimulating action of atom groups common to many different cells upon particular receptors likewise common to various cells for which they possess chemical affinities, resulting in the overproduction in the immune animal of such receptors. In the test tube, or even in the animal body, these may exhibit affinities for structures of very different morphology and function from those used for immunization, but which may, nevertheless, be more or less closely allied in chemical composition.

In the experiments here recorded active hemolysis was found to be the most characteristic property of the serum of rabbits into which the adrenal bodies of the guinea-pig had been injected, and affinity

for the adrenal cells was manifested only in the test tube by the power to agglutinate adrenal cells. By the methods used lysis of the adrenal cells in the test tube was not certainly seen. This, however, may be referable to technical omissions. In the studies of von Dungern[1] and of Moxter[2] with ciliated epithelium and testicular infusions hemolytic activity was also exhibited by the serum of the immune animals, though in both cases the sera contained, in addition, demonstrable specific principles; in the one case destructive for ciliated epithelium, in the other for spermatozoa, when injected with these cells into the peritoneal cavity of the guinea-pig.

These observations led both von Dungern and Moxter to regard the serum obtained by them as not strictly specific, but rather as having affinities both for erythrocytes and for epithelium and spermatozoa, respectively. Moreover, von Dungern observes that the serum resulting from immunization of animals with ciliated epithelium is equally active against the epithelium of the mammary gland,[3] both epithelial in nature, it is true, but still morphologically distinct. In commenting upon these observations both Metchnikoff[4] and his pupil, Metalnikoff,[5] maintain that von Dungern and Moxter are in error, that the hemolysis observed in these sera is referable to the blood unavoidably injected with the epithelial and testicular cells used by them. This position they endeavor to support experimentally by injecting animals with mixtures of spermatozoa and defibrinated blood. The result, as might have been expected, was a serum having both hemolytic and spermatoxic activities, and the specific receptors could easily be separated or removed. In all of our own efforts to produce an actively hemolytic serum, and so far as we can learn from the experience of others, it has been necessary to use very much greater volumes of defibrinated blood than would be mixed with the infusion of an organ to be employed in the preparation of a specific cytolytic serum, and the result of such an admixture is so well known to every worker in this field that one can scarcely conceive the neglect of special effort on the part of the experimenter to avoid it. That a certain quantity of blood was injected with the

[1] Münch. med. Woch., 1899, No. 38. [2] Deutsche med. Woch., 1900, No. 4.
[3] Die Antikörper, etc., von Lungern; Gustav Fisher, Jena, 1903, S. 30.
[4] Annales de l'Institut Pasteur, 1900, Tome xiv. pp. 4 and 373.
[5] Ibid., 1900, tome xiv. p. 581.

adrenals in our experiments there can be no doubt, but how much it is impossible to state with even approximate accuracy. It must, however, have been very small indeed, since the adrenal of the guinea-pig, though relatively vascular, is very small, and its absolute blood content must have been scarcely considerable, and of this amount some necessarily escapes on the removal of the gland. At all events we have under way a series of experiments to determine the minimum amount of blood necessary to induce an amount of hemolysis equivalent to that observed in our adrenal sera.

That the hemolysis exhibited by our "adrenal sera" is due to the small quantity of blood injected with the adrenal cells is, to us, questionable, for it was often as great, and even greater, than that exhibited by the blood of rabbits that had been purposely injected with relatively large doses of guinea-pigs' erythrocytes. Thus, for instance, in one of our comparative tests we found, taking the hemolytic activity exhibited by normal rabbit serum on washed guinea-pigs' erythrocytes as unity, that the serum from a rabbit that had received fifty-three cubic centimeters of defibrinated guinea-pigs' blood in broken doses by intraperitoneal injection, and was bled ten days after the last injection, was twice as active; the serum from adrenal Rabbit B also twice as active, and that from adrenal Rabbit D was five times as active, and yet neither of the animals furnishing the "adrenal serum" could have received more than the merest fraction of the amount of blood injected into the rabbit that furnished the "specific hemolytic" serum.

VIII. Studies upon the Active Principle of the Adrenal Bodies. In the course of his numerous contributions to the general subject of immunity and its underlying mechanism, Ehrlich has from time to time expressed the opinion that, while tolerance may occasionally be exhibited by animals to progressively increasing doses of certain definitely constituted poisons, this is not necessarily accompanied by the elaboration of anti-bodies, and cannot, therefore, in such cases be regarded as an immunity in the sense in which the word is to-day understood. This opinion has not been shaken by such experimental evidence as we have seen on the subject.

The studies that have been made upon the adrenal gland of different animals point to the elaboration of a something having at times marked toxic action, and through elaborate researches, especially of

Abel, a crystallizable body of definite chemical composition has been isolated.[1]

In the light of our negative results with the adrenal glands themselves we decided upon a study of the reactions of the rabbit to the active principle of the gland. These studies, though not yet complete, have, however, supplied information that is not without interest.

Through the courtesy of Professor Abel, to whom we here express our thanks, we had placed at our disposal a sufficient quantity of the active principle of the adrenal bodies to begin the work.[2]

It is needless at this time to enter into the details of the chemical nature of the substance supplied by Professor Abel. It suffices to say that it came to us in the form of a white amorphous powder, tolerably readily soluble in 1 : 1000 HCl when gently warmed, and gradually partaking of a more or less distinct violet color when exposed for a time to light and air.[3]

When used by us it was always in an acid solution made from the dried preparation not more than five or ten minutes before the injections. The convenient proportions for solution we found to be at the rate of two milligrams of the dried substance to one cubic centimeter of a 1 : 1000 solution of hydrochloric acid, and the mode of administration was always by direct intraperitoneal injection.

As stated, our problem was to determine, first, if tolerance to gradually ascending doses of the drug is exhibited by rabbits, and, second, if such tolerance is accompanied by the presence in the serum of anti-bodies having a restraining or neutralizing action upon the drug in the test tube or otherwise. Of fundamental importance to the success of such a study is a knowledge of the minimum lethal dose (M. L. D.) of the substance under consideration.

Notwithstanding a fair effort in this direction, we have found it impossible by the methods used to determine this factor. We have had full-grown rabbits die after so small a dose as one milligram, and have had some die and some recover after so large a dose as eight milligrams into the peritoneal cavity. (See Exhibit III.)

[1] For the literature upon this subject, see Amberg, Arch. int. d. Pharm. et d. Ther., 1902, vol. xi. p. 57.

[2] The experiments to be recorded were made with a single sample of the adrenal active principle, so that variations cannot be referred to variations in the material used.

[3] A letter received from Prof. Abel informs us that the material supplied for these experiments is what he proposes to designate as "epinephrin hydrate."

EXHIBIT III.—GIVING RESULTS OF EFFORTS TO DETERMINE THE M. L. D. FOR THE ACTIVE PRINCIPLE OF THE ADRENAL GLAND.

Rabbit.	Weight.	Dose in mgs.	Mgs. per kilo.	Result.
20	1650	1.0	0.8	Died next morning.
21	1400	1.5	1.1	Recovered.
24	1400	4.0	2.8	Died in two and a half hours.
32	1830	4.0	2.2	Recovered.
33	2230	4.0	1.8	Died in forty-five minutes.
34	2600	4.0	1.6	Recovered.
35	1820	6.0	3.3	Died in two and a half hours.
60	1870	6.0	3.2	Died in two hours.
41	2490	6.5	2.6	Recovered.
51	2210	8.0	3.6	Recovered.
52	2040	8.0	3.9	Recovered.
25	1720	12.0	7.0	Died in two and a half hours.

There is a corresponding irregularity in the manifestation of physiologic results in those animals to which the dose is not fatal. Some individuals appear to be profoundly affected after so small a dose as one-half milligram, while others exhibit no inconvenience from doses of from four to eight milligrams. One of the rabbits (No. 27), to which a total of twenty-eight milligrams was given in twelve daily doses, beginning with six-tenths milligram and gradually ascending in amount to four milligrams, was as much affected after the last as after the first dose, and was usually so much affected by the injections that for a time following each injection its recovery was doubtful, while two other rabbits in the same series (Nos. 28 and 30), injected at the same time with equivalent amounts, exhibited at no time, either early or late in the course of the experiment, anything more than a very slight acceleration of respiration that passed off in fifteen or twenty minutes, and was often even difficult of detection. Notwithstanding our failure to determine the M. L. D. for this substance, we began a series of immunization (?) experiments to observe the changes, if any, exhibited by the blood of those animals in which we hoped to detect a tolerance to the drug. Six mature, healthy rabbits were selected, regardless of weight, and each received daily intraperitoneal doses beginning with six-tenths milligram and gradually ascending to four and six milligrams in different animals. (See Exhibit IV.) All

EXHIBIT IV.—RECORDS OF RABBITS RECEIVING GRADUALLY INCREASING DOSES OF THE ACTIVE PRINCIPLE OF THE ADRENAL BODY. ALL INJECTIONS INTRAPERITONEAL. MARCH, 1903.

No.	Weight.	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
26	2770	0.6	1 1	1.2	1.4	1.8	2.2	2.5	3.0	3.3	3.6	4.0	4.0	+															
27	1740	0.6	1.0	1.2	1.4	1.8	2.2	2.5	3.0	3.3	3.6	4.0	4.0	...	...	...	...	...	Bl	...	...	...	...	...	...	...	...	6.0	+ in 15 min.
28	2190	0.6	1.0	1.2	1.4	1.8	2.2	2.5	3.0	3 3	3.6	4.0	4.0	4.0	4 0	4.0	...	6.0	...	...	...	...	...	...	...	...	...	6.0	* Recovered.
29	1870	0.6	1.0	1.2	1.4	1.8	2.2	2.5	3.0	3.3	3.6	4.0	4.0	4.0	4.0	4.0	...	6.0	...	...	...	...	...	...	...	...	...	6.0	† Recovered.
30	3420	0.6	1.0	1.2	1.4	1.8	2.2	2.5	3.0	3.3	3.6	4.0	4.0	Bl	...	...	...	...	...	...	...	...	...	...	...	...	...	6 0	* Recovered.
31	1820	0 6	1.0	1.2	1.4	1.8	2.2	2.5	2.0	3.3	3.6	4.0	4.0	4.0	4.0	Bl	...	...	...	...	...	...	...	...	...	...	...	6.0	† Recovered.
Control		...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	6.0	+ in 2 hours.

* Nos. 28 and 30 scarcely, if at all, affected. No. 28 found dead two days later

† Nos. 29 and 31 so seriously affected that they were not expected to recover; No. 31 died two days later.

\+ Dead. Bl. Bled.

lost weight during the course of this experiment, the loss ranging between three hundred and six hundred grams. After a total of twenty-eight milligrams one animal of the series died, with nothing at autopsy to account for death. Microscopically the adrenals were congested, but otherwise not changed. Five days after the last injection of another rabbit that had had twenty-eight milligrams in all it was bled and its serum tested for the presence of antitoxic substances. The day following the last injection of another rabbit that had also had a total of twenty-eight milligrams it was bled and its serum also tested, while on the day following the last injection of another rabbit that had had a total of thirty-six milligrams, blood was drawn and tests of the serum made.

These tests were made by mixing with that quantity of the drug that had most often proved fatal (dissolved in 1 : 1000 HCl) from two to four cubic centimeters of the serum from the treated rabbits. The experiments were controlled

By direct injections of the drug in four, six, and eight milligram doses dissolved in two, three, and four cubic centimeters, respectively, of 1 : 1000 HCl solution;

By the dilution of similarly dissolved doses with 0 85 per cent. NaCl solution in amounts equivalent to that represented by the serum mixture. This was sometimes injected at once, and again after two hours, at 38° C.;

By mixtures of similar doses with varying quantities of normal rabbit serum used at once, and after two hours at 38° C.; and

By mixing, as said above, of similar quantities of the toxic substance with different amounts of the serum from the treated (tolerant) animals; used, also, sometimes at once, and again after two hours, at 38° C.

One control was made with a volume of the hydrochloric acid (1 : 1000) alone to observe the effects upon the general condition of the animal. These were so limited in extent and of such brief duration as not materially to interfere with the correct interpretation of the results of injection of the drug in such a solution.

It is needless here to enter into the details of these experiments. They were negative throughout in demonstrating antitoxic properties in the serum from the treated animals, and were very much confused by the frequent failure of the drug, even in six and eight milligram doses, to cause more than a transient effect in the control animals.

In a number of cases the physiologic action of the drug was as marked in the animals getting the "specific" serum along with the drug as in those getting the drug alone or diluted with salt solution. The animals that got the mixtures of the drug and normal rabbit serum were neither more nor less affected than those that received the drug and "specific" serum.

By the method of administration and observation employed in these experiments the specific physiologic action of the drug is made manifest principally through respiratory disturbances. Within a few minutes after injection the rate of respiration is increased, and, after another ten minutes, has become so accelerated that it is impossible to determine its rate by counting. When in this condition the rabbit settles upon its belly or side, with its front and hind legs braced against the walls of its cage, its head thrown back, and its mouth, from which there is at times an excessive flow of saliva, partly open. It may remain in this position, if not molested, until death, or until the acute symptoms have passed off. This may be fifteen minutes or several hours, according to dose and individual peculiarities. In some cases the animal is constantly shifting its position, always giving one the impression that an effort is being made to assume a position best adapted to labored respiration. We have not seen paralysis in any of our animals, nor have we noted any affection of the bowels.

Usually there is marked urination immediately or shortly after the injections.

There has been no discharge of blood from the air passages of any of our animals.

Unless distinct physiologic effects are observed within a half hour after the injection, they are not apt to develop, and in none of our animals in which there was a delay of thirty to forty-five minutes in the appearance of the respiratory symptoms was there a fatal termination, no matter what the dose may have been. In three of our control animals, ranging in weight from 1740 to 2210 grams, to which eight milligrams each of the drug were given, there was practically no disturbance of the respiration. On the other hand, as said, many develop alarming symptoms after very much smaller doses.

The conditions found postmortem in those that die in from two to four hours after the injection are usually confined to the thorax. The

lungs are engorged with blood and the heart has the appearance of having been forcibly distended with blood.

The abdominal viscera may be normal, but are more often pale, almost blanched, in appearance.

In none of our autopsies have we discovered evidence leading us to believe that the material was injected elsewhere than in the peritoneal cavity. Punctures of the intestines and bladder were sought for, but none were encountered.

The most impressive feature of this group of experiments is the remarkable variation in individual susceptibility to the action of the drug, for which, unfortunately, there is no ready explanation. To assume that the mechanism by which the toxicity of the adrenal secretions are normally regulated during life varies with different individuals, being adequate in the one case to meet the demands made by the sudden artificial addition of unusual quantities of this toxic principle, while in others it is not, may be reasonable and logical, but not as yet supported by established facts, and has little more than speculative value in explaining the irregularity encountered by us and others.[1]

IX. Conclusions. The foregoing results seem to warrant the following conclusions :

1. It is doubtful if repeated injections of guinea-pig adrenals into rabbits result in the elaboration of a serum having demonstrable specific affinities for the adrenal glands of the guinea-pig *in situ*.

2. The most conspicuous characteristic of a serum obtained by the above plan is its destructive action upon the blood of the guinea-pig. This we do not believe is referable to the small quantity of blood injected with the adrenal cells during the immunization of the rabbit.

3. If the hemolytic receptors be removed from such an "adrenal serum," its toxic action upon the guinea-pig disappears.

[1] In a single experiment made with the serum of a rabbit after the intraperitoneal injection of dogs' adrenals we found a slight reduction in blood pressure of the dog to follow the intraperitoneal injection of this serum. Similar injections of dogs with normal rabbit serum, with normal sera of the duck and with the "adrenal serum" from the rabbit prepared with guinea-pigs' adrenals as above, all in doses of from ten to twelve cubic centimeters, had no appreciable effect upon blood pressure. The only significance of this observation is in connection with the negative results of the other studies here recorded. It suggests the possibility of positive results by a plan of analysis not taken up in the body of our work.

4. Rabbits exhibit more or less of tolerance to gradually ascending doses (intraperitoneal) of the active principle of the adrenal gland. This tolerance is probably not accompanied by the presence in the serum of the rabbits of substances antagonistic (antitoxic) to the adrenal active principle *in vitro*.

CHRONIC CYANOSIS, WITH POLYCYTHEMIA AND ENLARGED SPLEEN: A NEW CLINICAL ENTITY.

By WILLIAM OSLER, M.D.,
PROFESSOR OF MEDICINE IN JOHNS HOPKINS UNIVERSITY.

The group of cases here reported, with those collected from the literature, are worthy of careful study, as we have here in all probability "a definite clinical entity and one which is new to medical science," to use the words of Saundby and Russell in describing their case. The condition is characterized by chronic cyanosis, polycythemia, and moderate enlargement of the spleen. The chief symptoms have been weakness, prostration, constipation, headache, and vertigo. A further analysis will be reserved until after the consideration of the cases:

Case I. *Cyanosis for years, of unknown origin; albuminuria; rapid pulse; polycythemia; high muscular tension.*—Dr. K., aged forty-four years, consulted me October 28, 1901, complaining of a rapid pulse and diffuse cyanosis. He has been a very healthy man, active and vigorous, of good habits; has had no serious illnesses. He has been uneasy about himself, as he had detected a trace of albumin in the urine. For several years his wife has noticed that he has had a very congested appearance, and the eyes would often be deeply suffused. I have seen him at intervals for the past five years and have known him to be a very blue-faced man. He has been of a constipated habit. His eyes are somewhat prominent, but his wife says this is natural to him. He has constantly a feeling of fulness in the head, sometimes a sensation of vertigo, and for these symptoms he consulted me.

He was a well-built, well-nourished man; the face much suffused; the ears looked a little blue; the conjunctivæ were in-

jected, and the lips distinctly cyanotic. The tongue also looked cyanotic. The general surface of the skin looked suffused and the anemia left after pressure of the hand on the skin was very marked, and very slowly obliterated. The feet and hands were quite cyanosed. The radials and temporals were moderately sclerotic. Pulse 120, regular. Apex beat in fifth, just inside the nipple line ; sounds clear ; aortic second a little accentuated. There was no enlargement of the thyroid. No enlargement of the liver ; moderate enlargement of the spleen, the edge of which was palpable. The chest was well formed, not barrel-shaped ; the cervical muscles not prominent. Expansion of the chest good. No sign of emphysema. Expiration not prolonged. Once or twice he called on cold days to show the extreme cyanosis, and twice he came in with cough, which troubled him chiefly at night.

Several careful analyses of the urine were made by Dr. Futcher. The specific gravity ranged from 1012 to 1017 ; albumin was constantly present, as a rule, only a trace ; no sugar. On centrifugalizing there were a few hyaline and finely granular casts

I was very much puzzled as to the nature of this case, and thought that he had some chronic degeneration of the kidneys, with slight arteriosclerosis, but I did not think it could be advanced, as there was no marked hypertrophy of the heart, and the aortic second was not specially ringing. I could not account for the cyanosis.

Blood. The examinations were made by Dr. Futcher. Drop from ear almost black in color ; flows sluggishly. A striking feature is the slowness with which the drop spreads under the cover. With the usual-sized drop the field is found almost filled with red cells ; they look natural. Another striking feature is the relative scarcity of leukocytes. Red blood corpuscles, 9,952,000 ; leukocytes, 4000 ; hemoglobin, 120 per cent. (Fleischl). No measurements of the red cells were made. Several counts were made, as it was thought that there might have been a mistake.

Two observations of the blood pressure, taken on the right arm when he had been in the sitting posture for about ten minutes, gave maximum pressure, 203 mm. Hg; minimum pressure, 175 mm. Hg. Five minutes later the maximum pressure, 200 mm. Hg; minimum pressure, 172 mm. Hg.

I saw this patient repeatedly during 1902. There was very

little change in the condition. The cyanosis was always marked. He was able to attend to his practice. There was no shortness of breath ; the heart's action became slower. I once counted it at 72, but he said that it was often at 120 per minute. The last examination of the urine, November 14th, showed only a trace of albumin and a few hyaline casts. The spleen never became much enlarged, but it was always easily palpable. He went to California, and has since been under the observation of Dr. McBride.

Case II. *Recurring attacks of nausea and vomiting ; remarkable cyanosis, of some years' duration; pain in the side ; polycythemia ; albuminuria.*—M. C. (General Hospital Nos. 31202, 34970, 38753 40820, 42041), aged thirty-five years, a Russian Jew ; tailor by occupation ; admitted for the first time on July 11, 1900, complaining of constipation.

The family history was unimportant.

Personal History. The patient has always been well. Since coming to this country, six years ago, he has been pressing in a tailor-shop, and has had to work standing. He denies gonorrhea and syphilis. He uses alcohol moderately. Ever since coming to the United States, the patient has been troubled with constipation, the bowels never moving more frequently than every second day. This is worse in the summer. Three years ago, during the summer, the bowels on one occasion were constipated for fourteen days. There is no pain during these attacks. For a long time he has been dark in color ; he does not know for how long, but his friends have noticed it.

The patient's bowels moved eight days before admission after taking licorice powder. He had been constipated for four days previous to that. Seven days ago the patient began to vomit after each meal. He has vomited daily since. Castor oil, Epsom salt, and licorice powder have been ineffectual. There have been no other symptoms save that of drowsiness. The patient has voided very little urine during these eight days.

On examination the patient was a well-nourished man, with marked cyanosis of the face, hands, and mucous membrane ; the tongue was heavily coated.

The physical examination proved entirely negative, except for the cyanosis already noted. The temperature reached 102° shortly

after admission, and fell to normal by midnight and remained so. On this day the blood count was: Red blood corpuscles, 7,172,000; leukocytes, 21,800; hemoglobin, 120 per cent; no malarial parasites found; Widal reaction negative.

On July 16th the blood count was: Red blood corpuscles, 6,520,000; leukocytes, 14,400; hemoglobin, 102 per cent. The patient is feeling very much better and the bowels are moving regularly.

The patient was admitted for the second time on May 27, 1901, complaining of vomiting, which came on five days before admission. The patient admitted excessive indulgence in soda-water on the day of the illness. He states that he has vomited "every moment" since the onset, and that there has been some blood in the vomitus, which is very foul-smelling. The bowels have been constipated since the onset. He has eaten nothing for several days. There is no abdominal pain.

May 29th. Dr. Futcher noted that the cyanosis was still very marked, especially in the buccal mucosa, and that there was a marked pyorrhea alveolaris. Slight tenderness in the right iliac fossa. The spleen and liver were not enlarged.

27*th.* The blood count gave red blood corpuscles, 8,900,000; leukocytes, 23,000; hemoglobin, 125 per cent.

28*th.* Vomiting continues unabated. Calomel, cerium oxalate, and lavage have been ineffectual in stopping it. Analysis of the vomitus: total acidity, 85; free HCl, 37; no lactic acid.

29*th.* Red blood corpuscles, 10,200,000; hemoglobin, 112 per cent.

30*th.* Lips very livid; the general surface of the skin, including face, trunk, and extremities suffused. The imprint of the hand disappears very slowly, and the nails are a little cyanosed.

June 1st. Patient's bowels were finally moved by a high enema. The blood count was as follows: Red blood corpuscles, 7,576,000; leukocytes, 30,000; hemoglobin, 115 per cent.; specific gravity (chloroform and benzol method), 1068.

4*th.* The patient was discharged feeling greatly improved, the bowels having commenced to move somewhat more freely.

The patient was admitted for the third time on April 29, 1902, complaining of an attack of vomiting, hiccoughing, and constipa-

tion, which began seven weeks previously. He had vomited bile several times. The attacks of vomiting have lasted for ten or twelve days at a time and recurred repeatedly. The blood count on admission was as follows: Red blood corpuscles, 7,144,000; leukocytes, 8600; hemoglobin, 110 per cent.

On April 30th Dr. McCrea noted that the area of stomach tympany was slightly increased; cyanosis still present; considerable pigmentation of the skin. Differential count of the leukocytes: Polymorphonuclear, 79.4 per cent.; small mononuclear, 14 per cent.; large mononuclear, 2.4 per cent.; eosinophiles, 1.8 per cent.; transitionals, 2 per cent. A test-meal showed free HCl present; no lactic acid. On two successive days after a long fast, the stomach-contents were removed and revealed a fair amount of free HCl. The blood count on May 12th was little changed.

On May 22d the patient was discharged improved, the bowels moving regularly.

The urine had a specific gravity of 1010 to 1020, with a trace of albumin and a few casts, usually hyaline, but on one admission granular.

The fourth admission was on November 7, 1902, the patient stating that he was awakened at 4 A.M., three days before admission, with a pain in the left side, followed by vomiting, which has been continuous since. No blood in the vomitus. Constipation for five days. The patient has not eaten anything since the onset and has taken very little water. There has been some hiccoughing. Blood count: Red blood corpuscles, 7,316,000; leukocytes, 12,300; hemoglobin, 112 per cent. The cyanosis is still very marked. There is some dyspnea, vomiting, and hiccoughing. A differential count of the leukocytes shows a slight increase in the polymorphonuclears and a diminution in the small mononuclears since the previous record. The specific gravity of the blood is 1083.

November 12*th*. Red blood corpuscles, 8,300,000.

15*th*. Red blood corpuscles, 6,700,000. Coagulation time, one and a half minutes. Specific gravity, 1072.

19*th*. The vomiting persisted until two days ago, and the vomitus showed at all times free HCl; no lactic acid; slight starch digestion. The constipation was also very obstinate until yesterday. Discharged improved.

Patient admitted for the fifth time on January 28, 1903, and for the sixth time March 11th. On both of these occasions the chief symptoms were pain in the left side and the obstinate constipation. He says that the pain brings on the vomiting. The vomitus is at first frothy and white, later greenish in color. The pain is deep below the tenth and eleventh ribs on the left side, and extends toward the posterior axillary fold. On his last admission the cyanosis was extreme, the face was almost black, and the expression very anxious. There was no albumin in the urine, but on March 30th there were a few granular casts. The blood pressure was 125; the specific gravity of the blood 1081. The bowels were freely moved, and this always gives him relief. On the last admission there was very little vomiting, yet the cyanosis was never more marked.

May 25th. Patient has been keeping very well and is at work. He complains of pain in the left side, under the ribs, and says that as he walks he keeps his hand over the sore spot. The cyanosis is marked, quite as much as at any time in the hospital. The impression of the hand on the skin of the trunk remains a long time. The spleen is not palpable; the vertical flatness is about four inches in extent. He thinks that the skin has become darker.

Case III. (Dr. Lowman.) *Chronic cyanosis; enlarged spleen; polycythemia; headache; increased tension; albuminuria.*—While making a visit at the Lakeside Hospital, Cleveland, with Dr. Lowman, my attention was directed to a patient who was unusually cyanosed, and who had an enlarged spleen. On further examination the case was found to belong to the group under consideration. I am indebted to Dr. Darby, Dr. Lowman's first assistant, for the notes of the case.

Female, aged forty-four years, married, of English descent, admitted to the ophthalmologic division of the hospital for double pterygium, failing vision, and headache; for the latter she was transferred to the medical service. The condition of the fundi was negative, with the exception of tortuosity of the vessels.

The family history was negative.

She had had the usual infectious diseases. She had been a very healthy woman of good habits. There was no history of syphilis. She had not had winter cough or attacks of asthma. She has two

children living and well. For many years, she does not know how long, she has been blue. She has had no cough, no special shortness of breath on exertion. For four years she has had headaches, which have become more intense during the past four months. They begin over the left eye and extend backward and down the neck.

On examination the patient is well nourished, the skin is dark in color, and there is a general cyanosis, particularly marked on the face, arms, and upper part of the trunk; the feet and toes are blue. Everywhere the impression made with the finger disappears slowly. The conjunctivæ are suffused. The eyes are not specially prominent. There is well-marked pterygium. Looking more closely at the face there are some distended venules about the nose and cheeks. The lips are quite cyanosed, and the tongue and buccal mucous membranes have a dusky blue color. The radials are moderately sclerotic; the vessels seem full and the tension high. The apex beat of the heart cannot be felt; there is no visible shock; no enlargement upward or to the right. The sounds are clear; the second pulmonic is accentuated. The chest is not barrel-shaped. Percussion note is clear everywhere, and there are no bronchitic râles; no prolongation of expiration.

The abdomen looks normal. On palpation the spleen is enlarged, extending 7.5 cm. below the costal margin; the anterior margin and the notch are easily felt. The upper limit of flatness is on the eighth rib. The liver is not enlarged.

Blood. April 13, 1903, red blood corpuscles, 11,616,000; leukocytes, 5100. Differential count: Polynuclears, 59 per cent.; lymphocytes, 32 per cent.; mononuclears, 8 per cent.; eosinophiles, 0.5 per cent. Hemoglobin, 120 per cent. Specific gravity, 1067. A subsequent examination made on May 8th gave the red blood corpuscles, 10,692,000.

Urine. No excess of the daily amount; clear in color; specific gravity ranged from 1010 to 1016; reaction acid; a trace of albumin and a moderate number of hyaline and granular casts.

At my suggestion the patient was put upon sodium nitrite, and Dr. Darby writes, under date of May 8th, that the headaches have entirely disappeared.

Case IV. (Dr. Stockton.) *Chronic cyanosis; general weakness; headache and general pains, with attacks of weakness and shortness*

of breath; pigmentation of skin; death; autopsy.—When speaking of the condition with Dr. Lyon, of Buffalo, he mentioned a remarkable case of chronic cyanosis in the Buffalo Hospital under the care of Dr. Stockton, and on his return he found that there was polycythemia. To the former I am indebted for the following notes, and to the latter for permission to use them:

J. T., a Turkish Jew, aged forty-six years, married, a shoemaker, had been admitted to various Buffalo hospitals (General, Erie County, German, etc.) for several years on different occasions, and died in the German Hospital, Friday, May 1, 1903.

His chief complaint was general weakness, chronic headache; pain in the feet and legs, made worse by walking; general diffuse pains in the abdomen, pains also over the region of the heart, moderate chronic constipation, a slight cough, and occasional attacks of shortness of breath.

For about twenty years he has had a slight cough, off and on, worse in the winter and at night. Headache has troubled him for the same period (twenty years), and indefinite pain in the chest has been felt more or less during the past twenty years. His general strength had been of exceptional vigor until about six years ago, when it began to fail. About four years ago he began to grow much darker and bluer in his skin—cyanosed. Then he began also to have pains in different parts of his body, pain and a prickling sensation in the legs and feet, pain in the right chest and right shoulder; pain in the abdomen, not localized, but diffuse and general; headache continuing. The pain in different parts of the body was not constant, but shifted from time to time.

However, the headache and the pain in the legs and abdomen were present with tolerable constancy and have continued so up to his death. The pain was described as dull and aching. In addition to the pains, he had marked weakness during the last six years of life.

Constipation was never a marked feature of the case, though the bowels were generally sluggish. The appetite was poor and capricious. He had nausea occasionally, but never vomited.

During the past four years he had been going from hospital to hospital, spending a few months at a time in each, until he felt

better, then returning to his home and trying to work, but soon being required to return to a hospital because of his weakness, headache, body pains, and sometimes shortness of breath. In the hospital he would remain in bed most of the time, or sit quietly in a chair, occasionally walking slowly around the ward or going to the dining-room for his meals.

Cyanosis. The most striking feature of the case during the past four years has been a high-grade, extreme, general cyanosis, making the patient an object of general interest and curiosity in the various hospitals where he sojourned. His entire skin was dusky and bluish and his mucous membranes livid, resembling the appearance of a "blue baby" with congenital heart disease; in fact, he was jocularly called the "blue baby." This cyanosis was constant, though at times after rest in bed it improved somewhat, and again at other times was much intensified.

Pigmentation. The skin was generally dark and showed fine punctiform mottling or pigmentation, suggesting capillary extravasation as a cause, though no definite history of subcutaneous hemorrhages could be obtained. The naturally pigmented parts of the body were much more deeply pigmented than normal. The mucous membranes showed no appreciable areas of pigmentation.

Dyspnea. During the last three years of life he had occasional attacks of increased weakness, cyanosis, and dyspnea, his body becoming cold, so that his wife had often thought him dying. In the hospital, however, dyspnea was seldom marked, though the respirations were generally moderately increased.

Physical Examination. A short, stocky, well-built, and well-muscled man. Cyanosis as already noted. Pigmentation as already noted.

Heart. The heart sounds were always clear and without murmur at any time, but were generally rather weak, except the second pulmonic sound, which was somewhat accentuated. The heart's area by deep percussion was slightly enlarged to the left and right. In the sixth interspace, about one and a half inches to the left of the nipple line, could be seen an area of pulsation, the chest wall dimpling inward with each systole—*i. e.*, systolic retraction. This sign required a careful inspection to be seen.

Vessels. The arteries were soft and compressible. The veins were everywhere full and visible. There was slight throbbing of the vessels of the neck, above the clavicles, thought to be arterial.

Thorax. The lungs were everywhere hyperresonant on percussion, and the area of resonance extended downward at the bases behind somewhat, and in front on the right side the area of liver dulness did not begin until the seventh space was reached in the parasternal line. The area of resonance above the clavicles was not appreciably increased. On auscultation the breath sounds were soft and expiration was not prolonged. Occasional wheezes and sibilant râles could be heard over both lungs on different occasions during the last few months of life. (Dr. Thayer, who saw this case with Dr. Lyon, tells me that the state of the chest did not suggest to him emphysema.)

Liver. Flatness began in seventh space in parasternal line and extended vertically downward to about two inches below costal margin, where the edge could be felt.

Spleen. Never palpable, and its area on percussion was less than normal (perhaps explained by the emphysema of the lungs).

Abdomen normal.

Glands normal.

Legs. Occasionally very trifling edema was observed over the ankles, more distinct on the left side. No edema elsewhere was ever observed.

Eye Examination, February, 1903. Both disks hyperemic. Retina surrounding disks thickened. Vessels, particularly veins, engorged and tortuous.

Urine. An occasional trace of albumin; otherwise negative.

X-ray Examination of Thorax. Nothing abnormal except slightly enlarged heart.

Blood. The blood from the ear or finger-tip was on many occasions during the last few months of life examined and found extremely dark in color, and so thick that it would adhere to one side of thin filter paper without penetrating it. The depth of color and darkness of the blood was far beyond the range of estimation for hemoglobin by the color scales of the various hemoglobinometers. The red corpuscles were never counted until the day of death, when they were counted at 8,250,000. Differential leuko-

cyte count normal. Leukocytes were generally about 8300, never showing a hyperleukocytosis.

Pulse. The pulse was generally about normal, occasionally after exertion rising temporarily as high as 120 to the minute.

Temperature always normal.

Respirations. The general respiratory rate was from 22 to 25 per minute, once reaching 50 after severe exertion, with symptoms of collapse. On the afternoon of death the respirations were 38 per minute.

Death occurred on May 1, 1903, at 7 P.M., at the German Hospital in Buffalo, after three days' residence in the hospital. The patient died without any special symptoms or discoverable complications, in collapse and after a few hours of drowsiness deepening into semiconsciousness.

The full report of the autopsy is not yet available, but Dr. Lyon writes that the heart was about normal; the lungs showed moderate emphysema, with cyanosis and edema; the spleen was moderately enlarged. Nothing definite was found to account for the condition.

Cases from the Literature.

CASE V. (Vaquez, *Bulletin Médical*, Paris, 1902, vi., 849.)—Male, aged forty years. For ten years extremities cyanosed; veins distended. Then palpitations, dyspepsia, bronchial catarrh. Three years ago vertigo (Ménière type); buzzing and whistling in ears; staggering and eddying of objects; vomiting; no unconsciousness. Gums swollen, bleeding on irritation.

On examination, chronic cyanosis; no edema. Heart: No definite auscultatory phenomenon. Blood: Red blood corpuscles, 8,900,000; leukocytes, normal.

Second admission: Paroxysmal vertigo. Attack of pain in lumbar region, ended by discharge of red blood corpuscles in urine, lasting four to six days. Liver enlarged, 20 cm. in right mammary line. Spleen 24 cm. in extent. Urine, three liters daily; same amount of fluid as ingested. Blood: Finger, 8,450,000; elbow, 8,200,000, once 9,130,000; specific gravity, 1080; hemoglobin, 165 per cent.; hyperalkalinity of blood.

Pathology. Probable hyperactivity of hematopoietic organs, for of two cases of congenital cyanosis, one, with red blood corpuscles,

7,000,000, had a large spleen; the other, with 4,500,000, had no palpable spleen.

Case VI. (Cabot, *Boston Medical and Surgical Journal*, December 7, 1899.)—Female, aged forty-six years, widow, masseuse. Six years before admission she had sudden loss of consciousness, with settling of blood on one side of face and thick speech, which lasted several days. Four years later, after a period of hard work, she began to have periods of collapse, mental and muscular; face became purple, eyes injected; she was once thought to be drunk; vasomotor phenomena often present. Sciatica two weeks before admission; ecchymoses on thigh.

On examination, cyanosis of the face and tongue. Heart: No murmurs. Urine: Trace of albumin; a few hyaline casts. Blood: Red blood corpuscles, 10,460,000; leukocytes, 20,000; hemoglobin, 150 per cent. Heart apparently normal; pulse 90. No note on the spleen.

Course. Rested well in summer, but still cyanotic. Thyroid treatment had no effect. Later on, after tooth extraction, bleeding lasted half a day; made her better. Soon afterward she had attacks in which her legs began to move spontaneously, the feet moving around each other. A second attack on the train in two weeks. Soon weakness of left arm and leg, headache, vomiting. She died comatose.

Autopsy. Hemorrhage, middle meningeal; passive congestion of all the viscera.

Case VII. (Cabot, *Boston Medical and Surgical Journal*, March 15, 1900.)—Female, aged forty-nine years, spinster. Complaint, vertigo, weakness, bad taste, constipation. Blue line noted. Given potassium iodid and cascara.

One year later, trace of albumin and hyaline casts in the urine. Lead detected in the blood. Blood: Hemoglobin, 120 per cent.

Father died of "consumption of blood."

Otitis media at eighteen years; several attacks of reumatism. Menopause at forty-six years. Since then vertigo, palpitation, and headache; dizzy most of time. No tinnitus or nausea or eye symptoms. Cyanosis of lips for six months. Constipation. Four months ago three teeth drawn; then stomatitis set in. Itching at night. Polyuria.

On examination, cyanosis of face and mouth, hands and feet. Heart: Slight systolic murmur at pulmonary area. Spleen enlarged up and down. Hemoglobin, 120 per cent. In one week vertigo and cyanosis diminished. Hemoglobin, however, remained at 120 per cent. Four years later, red blood corpuscles, 12,000,000; spongy, bleeding gums; vertigo and staggering; skin bronzed. Lost twenty pounds in six years. Spleen a hand's breath below ribs. Red blood corpuscles, 9,252,000; leukocytes, 10,600; hemoglobin, 110 per cent. After venesection, red blood corpuscles, 10,032,000; normoblasts, 5. Later spleen reached to navel; red blood corpuscles, 11,352,000. Examination of gastric contents: No free HCl.

Case VIII. (McKeen, *Boston Medical and Surgical Journal*, 1901, cxliv., 610.)—Male, aged fifty-three years, German, packer in iron foundry.

Family history unimportant.

Personal History. Dyspnea twenty years ago, eight days; recurred at intervals of six months to two years. Alcohol, beer, and whiskey used moderately.

Present Illness. One and a half years ago cyanosis of face and hands following an attack of dyspnea. The cyanosis has persisted since, with exacerbations. Works right along; exertion causes no dyspnea or cyanosis. Every second or third day blurring of vision, sweating, vertigo, staggering; no headache or tinnitus. When blue the hands are cold and numb. For two years frequent attacks of diarrhea, sometimes with prolapsus recti.

On examination, no dyspnea; respirations 18 to the minute. Cyanosis of face, hands, and feet. Fingers clubbed. Erythema on shoulders and chest. Eyes congested. Tongue cyanotic. Gums swollen and bleeding. Many of the teeth loose. Arteries slightly thick. Heart, no murmurs. Lungs hyperresonant. Spleen one inch below rib, descending to two and a half inches on deep inspiration. X-ray showed emphysema. Urine: A trace of albumin, granular casts, red blood corpuscles, and leukocytes. Blood: Red blood corpuscles, 9,380,000 to 9,840,000; leukocytes, 9000; hemoglobin, 120 per cent.

Case IX. (Saundby and Russell, *Lancet*, 1902, i., 515.)—Male, aged forty-three years, an electroplater. First visit on April 13,

1891, complaining of pains in body, especially abdomen; headache for three or four months. Spleen enlarged. Urine: Specific gravity, 1010; a trace of albumin; no casts.

Second visit on January 29, 1898, complaining of cyanosis.

Family History. Mother died of phthisis.

Personal History. Syphilis at nineteen years, gastric fever at twenty-four years, later jaundice.

Present Illness. Eight months ago pains, gnawing, in abdomen, worse in morning; no vomiting, constipation. For six weeks loss of flesh and weakness.

On examination, dull, speech thick, memory and attention poor. Cyanosis of face. Fingers clubbed Teeth bad. Bronzing of legs. Spleen extends to middle line and navel; hard, slightly tender. Heart: No murmurs. Red blood corpuscles, 9,000,000; hemoglobin, 120 per cent. Once a few hyaline casts. He grew drowsy, jaundiced, and cyanotic. Later, red blood corpuscles, 7,360,000.

Autopsy. Hypertrophy of left ventricle. Spleen, 1440 grams; consistency normal. Brain congested. Suprarenal small, dark, soft. Thymus not noted.

Weil (*La Semaine Médicale*, June 29, 1901) has a brief note on two cases of hyperglobulism, with cyanosis, lasting from birth, in two children, one aged two years, the other four years. The blood count is not given. In one the spleen was enlarged, in the other normal. No heart disease.

Analysis of the Cases.

Six of the patients were males and three females. All were in the middle period of life, the youngest thirty-five years and the oldest fifty-three years. There was nothing in the occupation or in the station of life of any moment. The features may be considered in detail.

Cyanosis. Naturally this attracts most attention and has been the feature which has led to further investigation. As is usual in all forms of cyanosis, it is most marked about the face and hands, but in Dr. Lowman's case and in both of my patients the skin of the entire body was of a dusky blue. When first seen the suffusion of the conjunctivæ and the prominence of the eyes, as in Case I., may add to the startling appearance of the patient. The cyanosis

is more intense in cold weather, and is aggravated by any existing bronchial catarrh. On bright, clear days, with but little moisture in the air, it may lessen greatly, as in Case I. The period over which the cyanosis has been noticed varies from ten years (Case V.) to three or four years (Case I.). While constant, as a rule, it may vary greatly in intensity. In Case II. the patient usually came in very deeply cyanosed, the condition aggravated, no doubt, by the vomiting and the loss of liquids, but after a few days, when the bowels were moved, the color became less intense; but I saw this patient only the other day, some six weeks after his last attack of nausea and vomiting, and he was intensely cyanosed. There is no respiratory distress with the cyanosis. While the skin looks full and tense and the face and hands bloated, yet marked dilatation of the larger superficial veins is not noted. On close examination of the skin, many fine, dilated venules are seen.

Blood. The viscidity is greatly increased. All observers have remarked not only upon the unusually dark, but upon the thick and sticky character of the blood drop. An extraordinary polycythemia is a special feature of the affection. The maximum blood count was 12,000,000 per c.mm. in Cabot's second case. In eight of the cases the count was above 9,000,000 per c.mm., and in the ninth (Case IV.) it was 8,250,000 per c.mm. There have been no measurements of the red blood corpuscles. The statement is made that in the polycythemia of congenital heart disease the red blood corpuscles are smaller than in that of high altitudes. The percentage of hemoglobin has been high, ranging to (Case V.) 165. Usually the range has been from 120 to 150. In Case IV. it is stated to have been above the scale. The specific gravity of the blood in Case V. was 1080, and in Case II. it ranged from 1067 to 1083. In eight of the cases the leukocyte count ranged from 4000 in Case I. to 20,000 in Case VI. As a rule, in a majority of the cases it has been below 10,000 per c.mm. In Case II. on one admission the count reached 30,000 per c.mm.

Spleen. In seven of the nine cases the spleen was enlarged. In four of these the enlargement may be termed great, reaching nearly to the navel. In Case VI. there was no note. In Case II. it was not enlarged.

The liver was enlarged in Case V.

Urine. In seven of the cases a trace of albumin was noticed, with hyaline, sometimes granular, casts. In Cases V. and VII. there was no note on the urine. The specific gravity was usually low.

Pigmentation of the Skin. As might be expected from the prolonged existence of the cyanosis, the skin was noted to be pigmented in several of the cases (II., III., IV., VII., IX.).

Symptoms. The symptoms have been very varied. Most of the patients have complained of headache, weakness, and prostration. Headache was a prominent symptom in four cases, vertigo in four, constipation in four, pains in back and abdomen in three cases. Attacks of nausea and vomiting were a special feature in Case II., and are mentioned as present in Case V. Cough and shortness of breath were each present in one case. Fever was not noticed in any of the cases. The pulse was noticed to be of high tension and the vessels sclerotic. There was no edema of the skin. The torpor, mental and physical; the sensation of fulness in the head, with headache, vertigo, and in some cases nausea and vomiting, remind us of the symptoms to which mountain climbers and aeronauts are subject. Three of the cases were fatal. In Case IV. the patient died in collapse after a few hours of drowsiness. In Case VI. the patient died comatose with cerebral hemorrhage. In Case IX. the patient became drowsy and died in coma. The autopsy in Case IV. showed the heart to be about normal, moderate emphysema of the lungs, with cyanosis and edema and moderately enlarged spleen. In Case VI. there was passive congestion of all the viscera and hemorrhage from the middle meningeal artery. In Case IX. there was hypertrophy of the left ventricle, with congestion of the brain.

Remarks. *Chronic cyanosis*, a common enough feature in clinical work, is met with:

1. In organic disease of the heart, particularly in congenital malformation, in chronic myocardial and tricuspid lesions in children and adults, and in cases of adherent pericardium.

2. In certain diseases of the lungs, particularly emphysema, and in long-standing pulmonary tuberculosis of the fibroid type. Practically there are only two conditions in which patients walk into the hospital or into our consulting-rooms with extreme cyanosis, congenital heart disease, and emphysema.

3. In the methemoglobinemia of chronic poisoning with coal-tar products, as antipyrin and acetanilid, etc. In this condition, too, the patient may startle one by the markedly cyanotic appearance.

There are a good many people whose normal condition is one of great fulness of the bloodvessels of the skin, so that in cold weather there may be marked cyanosis of the ears and of the face. We all know the stout, hearty, full-blooded man with rubicund face—the type which has been well described by Clifford Allbutt in his *Lane Lectures*—a common one among draymen and in men of that class, who live much in the open air and who drink freely. In them cyanosis, though not necessarily present, may be very marked in the face and hands when the temperature is low. As a rule, the peripheral circulation is active and the normal condition is a vivid hyperemia of the skin associated with dilatation of numerous small venules.

Cyanosis, local or general, indicates one fact—diminished oxygenation of the blood corpuscles. In the deepest cyanosis of the ear or of the finger-tip the blood count may not be above 5,000,000 per c.mm. Only recently Dr. Futcher examined for me the blood of a red-faced, short-breathed Englishman, whose skin seemed fairly bursting with blood and whose fingers and ears were quite cyanosed. The red blood corpuscles were only just above 5,000,000 per c.mm. In the local cyanosis of Raynaud's disease the blood count may be very little above the normal. I have a patient at present in the wards in whom the blood count from the cyanosed foot ranges from 4,500,000 to 6,500,000; the count from the ears about 5,500,000 (Dr. Briggs). A few weeks ago, in Dr. Brayton Ball's wards of the New York Hospital, I saw an interesting case of coma (which turned out to be due to a fracture of the skull) with the most intense localized cyanosis in the fingers of one hand, active, vivid red hyperemia of the fingers of the other hand, and normal-looking blood distribution in the ears. The count, very kindly made for me by Dr. N. B. Foster, was practically normal and the same in all three situations. Contrariwise, the anomaly

[1] I am sorry I have not got a blood count in a case of this sort. As a rule, there is anemia; in a remarkable case which I saw with Dr. T. R. Brown, the hemoglobin was only 50 per cent. Unfortunately no count was made of the red blood corpuscles. In the case of a physician with extreme cyanosis from long-continued use of antipyrin, a blood count was made, and I remember that the red corpuscles were not above normal, but I have not the actual figures.

may be present (though I must say it is rare) of a red face and general superficial hyperemia with a very low blood count. During this session there has been under my care in Ward E a patient with what we have termed *anemia rubra*. With a blood count of about 2,000,000 per c.mm. from ear-tip or finger-tip, he was as red as a beet, and it was not until his blood had fallen to nearly 1,200,000 that he began to present a typical picture of pernicious anemia. On admission, with his blood at a little above 2,000,000, and looking the healthiest patient in the ward, he had nucleated red blood corpuscles. In the cyanosis of emphysema and the ordinary forms of heart disease, the number of red blood corpuscles per cubic millimeter is not, as a rule, much increased, and rarely reaches the limit of polycythemia, which, as suggested by Cabot, may well be placed at 7,000,000. Occasionally most extraordinary cyanosis occurs in adherent pericardium, as in a case reported by me (*Archives of Pediatrics*, 1896) and in the case reported by Lorrain Smith and McKisack (*Transactions Pathological Society*, London, 1902). In the latter the blood count was 6,000,000.

Polycythemia. There are two classes of polyglobulism—*relative*, in which the condition is due to a diminution in the quantity of the plasma of the blood, and *true*, in which there is an actual increase in the number of blood corpuscles. Much work has been done of late years on the subject. Relative polycythemia is very common. It may be caused by a deficient amount of fluids ingested, which possibly may be the cause of polycythemia of the newborn; more frequently it is caused by loss of liquids, either by (*a*) sweat; (*b*) diarrhea (by far the most common); (*c*) increased diuresis. (*d*) In another group of cases there is loss of liquids by secretion or transudation, as in narrowing of the pylorus with dilatation of the stomach, and in the constant loss of liquids from the blood in recurring ascites. It is interesting to note that in some of these cases the polycythemia is of a high grade and may persist for months or even for years. It is not necessarily associated with cyanosis, as in cases of dilated stomach and in diarrhea. There is also a toxic polycythemia described in poisoning by phosphorus and carbon monoxide, which, too, is probably relative. The polycythemia of vasomotor disturbances, such as has been determined by Becker, Thayer, and others after the cold bath and after violent exercise,

also comes in this class. Where the much-discussed polycythemia of high altitudes should be placed is by no means certain. While a number of observers hold that there is new-formation, the lack of oxygen acting as a stimulus, others believe that it is relative, and due to increased elimination of fluids from the body, or that it is entirely due to a large number of corpuscles in the peripheral circulation. Others, again, think it is entirely due to the effects of decreased atmospheric pressure. The microcytes, poikilocytes, and nucleated red blood corpuscles point to new-formation, but the question is still under discussion.

True Polycythemia. Vaquez and his pupil, Quiserne (*Thèse*, Paris, 1902), limit to this class the condition in which with an increased formation there is a continued increase in the number of red blood corpuscles in the circulating blood. It is met with where there is difficulty in proper aëration of the blood, as in high altitudes, or in heart disease, congenital and otherwise; and also in the obscure cases of the form here under consideration. The polyglobulism is regarded as a mode of adaptation to the new conditions and a sort of functional reaction of the organism. Belonging to this group is the polycythemia so readily studied in congenital heart disease, and described by Krehl, Gibson, and others. The figures often reach as high as 8,000,000 or 9,000,000, rarely so high as in the form discussed in this paper.

It is by no means easy to offer a satisfactory explanation of the polycythemia with cyanosis here under consideration. It does not seem possible to connect it in any way with the moderate grade of enlargement of the spleen, and yet there are one or two observations in the literature which are of great interest in this connection. Rendu and Widal (*Bull. et mém. Soc. méd. des hôpitaux*, 1899, 3 s., xvi. 528) report the case of a policeman who had an attack of vomiting without apparent cause, with dyspnea. The temperature was normal. Red blood corpuscles, 6,200,000; leukocytes, 6000. This count gradually diminished. On examination, skin subicteric; cyanosis of face and hands marked, to a less degree all over the body. A tumor, evidently the spleen, reaching from diaphragm to iliac crest. Eventually ulcers developed on tongue and the liver became enlarged. Autopsy: Spleen adherent to diaphragm, fibrous on section, and filled with caseous masses.

Moutard-Martin and Lefas (*Société des hôpitaux*, 1899) have also reported a case of a woman, aged forty-nine years, with pain in the left hypochondriac region, emaciation, no ascites, no cyanosis, with enlarged spleen, slight albuminuria. The red blood corpuscles were 8,200,000, the leukocytes 31,428. At the autopsy the spleen weighed 750 grams and contained large caseating nodules.

With our imperfect knowledge of the physiology of polycythemia it would be premature to discuss at any length the pathology of this remarkable group of cases. We need :

1. A careful study of all forms of chronic cyanosis with polycythemia, particularly those associated with heart disease and emphysema. (It is to be noted that the cases here reported have the highest blood count on record, much higher than the average in congenital heart disease or in dwellers at great altitudes.)

2. A more accurate study of the blood in this class of cases—the volume, the viscosity, the state of the plasma and the serum, the amount of hemoglobin, the specific gravity, and the diameter of the corpuscles. As increased viscosity of the blood, with resulting difficulty of flow, seems the most plausible explanation of cyanosis, it is especially important to test the viscosity by accurate physical methods and to determine the relation of the number of corpuscles to the viscosity of the blood.

3. The relation of the splenomegaly to the cyanosis and polyglobulism should be carefully observed. It may not be anything more than the effect of the chronic passive congestion.

Future investigation will determine whether we have here in reality a new disease. The clinical picture is certainly very distinctive; the symptoms, however, are somewhat indefinite, and the pathology quite obscure.

DISCUSSION.

Dr. Cabot: I have reported previously two cases of polycythemia, one with and one without splenic enlargement (*Boston Medical and Surgical Journal*, December 7, 1899, and March 15, 1900). Further details of the former of these are as follows:

Case I.—Florentine S., aged forty-nine years, rubber worker; single. Father died of "consumption of the blood." Family history not otherwise

remarkable. First hospital entry, January 22, 1895. Climacteric in 1891. Came to Out-patient Department January 5, 1894, with symptoms as described below. Paroxysms of headache and vertigo off and on for six years have troubled her. Palpitation and distress in cardiac area, with dyspnea on any exertion or excitement for seven to eight years. No edema. Chronic constipation. Six months ago a friend noticed blueness of the patient's lips and ulcerations about the gums were troublesome. Last year black and blue spots came out on the body. Itching for a few days.

Examination. Very marked cyanosis of face and mouth, hands and feet. Fingers not clubbed. Conjunctiva much injected, also pharynx. Gums angry red, and bleed very easily. Heart and lungs negative. Liver and spleen easily felt. Marks of scratching over trunk and extremities. Temperature, pulse, and respiration normal. Urine: pale, 1010, slight trace of albumin and of bile. Considerable lead. Few hyaline casts. Hemoglobin, 120 per cent. Spectroscope shows two bands of oxyhemoglobin and no others. Blood-stained saliva frequently expectorated. After a week the liver no longer palpable.

June 12, 1899. Since last entry (one year ago) "inflammatory rheumatism" in feet with swelling and blueness. The patient now says that the general cyanosis has been noticed constantly since 1893. Cuts always heal up blue. The attacks of vertigo have continued and are accompanied by nausea and eructations lasting about fifteen minutes and recurring every two to four weeks. Gums have been spongy and bloody ever since 1894, with offensive breath. At previous entry weighed 103 to 106 pounds; now 99 pounds.

Examination. Liver palpable about three fingers below costal margin. Spleen a hand's breadth below the ribs.

12*th.* Red cells, 9,252,000; whites, 10,000; hemoglobin, 110 per cent.

15*th.* Red cells, 10,032,000; whites, 5800; hemoglobin, 120 per cent.

16*th.* Venesection. Differential count of 500 leukocytes showed: Polynuclears, 80.8 per cent.; lymphocytes, 15.2 per cent.; eosinophiles, 3.2 per cent.; mast-cells, 0.8 per cent.; 5 normoblasts.

19*th.* Right great toe swollen, red, and tender. Venesection. Blood count taken from the spurting stream showed 9,580,000 red cells per c.mm.

22*d.* Red cells, 10,800,000.

July 16*th.* Discharged relieved.

December 6, 1899. Re-entered. Up to a month ago troubled with pain and stiffness in right knee and foot and in splenic region.

Examination. Hands and face now a brownish-blue, and folds of axillæ pigmented. Liver as before. Spleen extends to navel.

6*th.* Reds, 11,352,000; whites, 8300; hemoglobin, 105 per cent. Differential count of 400 leukocytes showed: Polynuclears, 77.25; lymphocytes, 18.75; eosinophiles, 2.75; myelocytes, 1.25; mast-cells, few; 2 microblasts, 2 normoblasts. Urine, average, fifty ounces; normal color; specific gravity, 1011; albumin, 0.1 per cent. (Esbach). Urea, 1.26 per cent. Few hyaline

and granular casts with cells adherent. Veins in fundus oculi four or five times their normal size and very dark. Stomach holds forty-eight ounces. Hydrochloric and lactic acid absent on two occasions one hour after an Ewald meal. Leukocytes before eating, 10,400; two and a half hours after eating, 11,700.

19*th*. Red cells, 10,230,000; whites, 8800; hemoglobin, 110 + per cent.

November 19*th*, 1901. Re-entry. Gets up two or three times at night, for the last two or three years, to pass urine. Weight, 100 pounds. Several attacks of "rheumatism" since leaving hospital—ankles and knees stiff and swollen for two or three months at a time. For the past six or seven months feet have swollen considerably and dyspnea is increasing; cannot sleep on left side. Liver as before. Spleen three inches below the navel. Notch felt.

20*th*. Red cells, 10,280,000; whites, 15,000; hemoglobin, 100 + per cent.

24*th*. Red cells, 10,560,000; whites, 14,400. Polynuclears, 83.4 per cent.; lymphocytes, 16 per cent.; eosinophiles, 0.6 per cent.

December 1*st*. Red cells from ear, 11,488,000; red cells from toe, 11,398,000. Urine, forty ounces; specific gravity, 1014; albumin, 3.5 per cent.; few hyaline and granular casts; urea, 1.27 per cent.

Dec. 2*d*. Bled six ounces, with considerable relief.

April 30, 1902. On crutches from "rheumatic" pain.

August 11*th*. Died after a week's diarrhea.

Case II.—James R., aged twenty-nine years, rubber mill, 6 Shaw Street, Providence, R. I., February 5, 1900 (seen by kindness of Dr. R. H. Fitz in his wards). For eight or nine years subject to attacks of abdominal pain said to be gallstones or indigestion. In March, 1899, noticed a lump in splenic region. Lost fifteen to twenty pounds in a year.

October 27, 1899. Dr. H. G. Palmer, Providence, found red cells, 6,640,000; whites, 18,400; hemoglobin, 95 per cent. Differential count normal.

Examination. Mucous membranes very bright colored. Liver dulness at fifth rib—edge felt below rib. Splenic dulness begins at fifth rib in anterior axillary line. Edge felt four finger-breadths below ribs.

February 8*th*. Red cells, 8,484,000; whites, 17,600. Differential count of 500 leukocytes showed: Polynuclears, 90.4 per cent.; lymphocytes, 8 per cent.; eosinophiles, 0.6 per cent.; mast-cells, 1 per cent.

10*th*. No discomfort. Discharged.

Dr. F. C. Shattuck: I have seen at least three cases of this kind. Two have been attended by Dr. Cabot. The other, the first in point of time, was told by his physician in Providence that he had Bright's disease. This diagnosis was repugnant to his wife, an ex-schoolmistress, and the physician was discharged. His urine was submitted to Professor E. S. Wood, who referred him to me, and he was under my observation for several years. The urine showed the characteristics of chronic interstitial nephritis. Cyanosis was marked when I first saw him, but later became intense. For months he spat up blood every morning, so great was the congestion of the throat. One

Saturday night, without apparent cause, he bled profusely from the upper intestinal tract. The amount of blood vomited was estimated by his physician, a competent man, as at least a gallon. I saw him about twelve hours later and found him in excellent condition, relieved rather than weakened by the blood-loss; cyanotic still, though less intensely so. The liver and spleen were enlarged, probably from congestion. Twice, I think, Dr. Cabot made a blood count for me. That from the ear had about ten, that from the foot about twelve million red cells. He finally died from gangrene of the foot following embolic occlusion of a leg artery. There was no autopsy.

In another case, recalling the relief following the blood vomiting in this one, venesection was repeatedly practised, as Dr. Cabot says, promoting comfort.

Dr. Stockton: I wish to put on record a similar case, which was studied for two successive years in the wards of the Buffalo General Hospital, in the service of both Dr. Cary and myself. The patient was a native of Turkey or Armenia, and had naturally a dark skin; however, there was never a question as to the very striking cyanosis. The facts of the case that I particularly recall are as follows: There was a trace of albumin, with occasionally hyaline casts; his counts of red cells showed from 7,000,000 to 8,500,000. He frequently raised small quantities of blood, sometimes blended with mucus, and had slight dyspnea on exercise. One of the most interesting features was the continued distress of which the man complained. His statements were vague and he located his suffering in various regions—the head, chest, and abdomen. I would like to ask Dr. Shattuck just what he means by the relief obtained in his patient from venesection? My patient suffered from apprehension and distress that was pitiable. Just before this meeting I learned that the patient had died at another hospital, and, to my regret, an autopsy was said to be unobtainable.

(It has since been learned that a postmortem was made. A moderate vesicular emphysema, a corresponding dilatation of the right heart, and slight enlargement of the spleen were found. The details of the case will doubtless be published.)

Dr. McPhedran: I saw a patient, aged thirty-four years, under the care of Dr. Thistle, two years ago who had extreme cyanosis such as the cases described by Dr. Osler, and in addition to that a bronzing or pigmentation of the skin. She was in the hospital a couple of times complaining of debility and some dyspnea on exertion. Examination revealed nothing abnormal. The spleen was much enlarged, and the blood count showed about what has been described to-day. There was some albuminuria. The heart was normal. She died some months later, and autopsy revealed nothing to determine the cause of death.

I think that cases of anemia with high color are more frequent in our more northern climate. In fact, so commonly is high color associated with anemia that all cases, especially ladies, of high color may be considered anemic unless

examination of the blood shows such not to be the case. High color depends rather on a low vasomotor tone than on the quality of the blood, and the color is, therefore, usually subject to rapid variations.

Dr. Hare: I have had a case in my ward that corresponded to the cases described by Dr. Osler, in which I was unable to make a diagnosis. It occurred in a coalminer, who had a polycythemia of 7,000,000, with enlargement of the spleen and albuminuria and constant cyanosis. I supposed there was a growth in the mediastinum which pressed upon the vessels and interfered with circulation, and thought the albuminuria was due to stasis in the kidneys. I looked upon it as a case of grave disease of the internal organs the cause of which could not be discovered.

The point as to the polycythemia of high altitudes is, I think, not universally accepted. Dr. Stengel has positive views about that matter, I know. The experiments that have been done with animals in this regard have been very contradictory. In most of the cases, I believe, after the first few weeks of residence in high altitude the polycythemia diminished.

Dr. Norman Bridge: The first patient whom Dr. Osler mentioned in his paper is now under my care. He is still deeply cyanotic. He has slight protrusion of the eyes, and his blood count is about 8,000,000 reds. He has had a good deal of headache during the last three months, such as is not uncommon in Bright's disease. Albumin is present in considerable quantity in the urine, and numerous hyaline casts can always be found. His total solid output of urine averages about 600 grains, and the urea about 300. He has improved somewhat by rest and outdoor life as to the headaches, but not otherwise. He has taken for a long time one-fiftieth of a grain of calomel three times a day.

I recall another case in a woman where cyanosis existed for a number of years. She had no enlargement of the spleen or liver, and no disease of the kidneys, but she was a sufferer from malnutrition and neuralgia. Suspecting that the large amount of coal-tar preparations which she had taken was responsible for the cyanosis, I begged her to stop them entirely, which she declares she has done for three months, yet the cyanosis is present to a slight degree. Her blood count at the height of the symptom showed 4,500,000 reds; 7000 whites. The hemoglobin was 64 per cent.

Dr. Stengel: I have recently reported a case of chronic cyanosis that was found to be due to taking acetanilid for a long time. The blood picture was so striking that the taking of the drug was evident, and she was forced to a confession.

A second case that came under my observation I have reason to believe is suffering from the same cause, although it does not show the same blood picture. The patient confesses to having taken some proprietary medicine for a long time. The cyanosis is not very great, and the polycythemia is not

beyond 7,000,000, but persists. There has been no degeneration of the red blood corpuscles.

I mention these cases in conjunction, because the first was evidently due to a hemolytic poison. In the second I suspected the same sort of an agency, though the persistence of the cyanosis after the patient, who is an intelligent man, denied the use of such a drug, and the absence of the characteristic blood picture, made the diagnosis less certain. These circumstances suggested to my mind the possibility of chronic cyanosis being due to a destructive agent without showing in the blood any manifest evidence of hemolysis.

In the first case there was enlargement of the spleen, which disappeared on withdrawal of the drug. When I was first called to see her and found her in a condition of extreme cyanosis I tried venesection, and with great benefit.

Dr. Edson: Dr. J. N. Hall reported a case identical with Dr. Osler's description: a middle-aged woman, who came into his office blue in color. He found no emphysema or cardiac difficulty on examination—only a blood count of between ten and eleven millions.

Dr. Joslin: A similar case has been under my observation for nearly a year. The nephritis was present and the eyes prominent. The patient gained over 50 per cent. in weight, the renal condition improved, and the pulse diminished in tension. She is now quite comfortable, though blind. I append the history of the case:

Sarah S., aged thirty-seven years; married; born in Russia; entered House of the Good Samaritan June 17, 1902. Family history and past history negative. Two healthy children. Six years ago "stomach trouble" of indefinite nature. On October 16, 1901, she entered the Boston City Hospital, with pain and tenderness in left hypochondrium. The spleen reached 3 to 4 cm. below the costal margin. Dulness and râles at both apices. Eyesight poor; weakness; thirst.

Blood. Hemoglobin, 100 per cent.; reds, 8,160,000; whites, 12,800.

May 12, 1902. Entered Massachusetts General Hospital, where she was operated upon on account of the pain. The spleen was found enlarged, nodular, completely anchored by firm adhesions, and the tip showed a peculiar white appearance. A piece of this was removed and examined by Dr. Wright, who reported an anemic infarct. A few adhesions were separated and one or two vessels tied. The gall-bladder, pancreas, and intestines were negative. The stomach was "wine-colored," but otherwise normal.

28th. Headache; eyesight failing fast; eyes are prominent; no enlarged thyroid; good appetite.

June 17*th.* The patient first came under Dr. A. K. Stone's and my observations. She was emaciated, moderately cyanotic, the veins and tortuous temporal arteries prominent; slight edema of the eyelids, especially the right;

pupils equal, but do not react; blind; lungs negative and remained so. Heart: apex in fifth interspace, left mammillary line, with a forcible, heaving pulsation which contrasted markedly with the flabby muscles in other parts of the body; aortic second accentuated; arteries are all much thickened and the pulse of high tension; the abdomen showed the laparotomy scar and a freely movable right kidney. The spleen extended from the eighth rib to the costal margin and was plainly felt; marked edema of feet.

Urine: 1575, neutral, normal; specific gravity, 1010; albumin, one-fourth per cent.; no bile; no sugar; granular and fatty renal cells; hyaline cast.

July 22d. Blood: Reds, 10,000,000; hemoglobin, 100 per cent. The examination of the eyes by Dr. Cheney showed an old optic neuritis; disks atrophic, borders completely obliterated; very little swelling; veins moderately tortuous; numerous retinal hemorrhages.

The patient slowly gained in weight and strength until November 4th, when phlebitis occurred in the left leg without known cause. It spread to the superficial veins of the left half of the abdomen, extending nearly up to the spleen. It was accompanied with little fever and much less pain than is usually the case. By December 10, 1902, the patient was again in good condition.

January 16, 1903. Heart: apex, fifth space, 1 cm. within mammillary line; pulmonic second louder than the aortic second; pulse tension nearly normal; spleen cannot be palpated.

Urine: August 15, 1902, 2830 c.c.; specific gravity, 1010; one-sixth per cent. of albumin; a few granular and hyaline casts. September 5th, 2000 c.c; specific gravity, 1010; large trace of albumin; a few granular and hyaline casts. November 4th, specific gravity, 1011; slight trace of albumin; a few granular and hyaline casts. January 16, 1903, 2100 c.c.; specific gravity, 1011; an occasional slight trace of albumin; fine granular cast.

Blood (see above): November 4, 1902, reds, 7,270,000; whites, 22,870; phlebitis. December 2d, reds, 6,960,000; whites, 22,600. February 10, 1903, reds, 8,376,000; whites, 14,800; hemoglobin, 95 per cent. March 27th, reds, 9,600,000; hemoglobin, 100 per cent.

Weight: July 19, 1902, 73¼ pounds; August 15th, 73¾ pounds; September 5th, 76¾ pounds; February 27, 1903, 107½ pounds; March 13th, 111¾ pounds. Condition as at last entry.

[NOTE.—The further development of the case will be reported in the *Boston Medical and Surgical Journal* by Dr. A. K. Stone or myself.]

DR. S. SOLIS COHEN: I should like to ask some questions, which may, perhaps, be answered later, in regard to the spectroscopic characteristics of the blood and in regard to the large hemoglobin content. Cyanosis and large hemoglobin content seem to be in a measure contradictory. I should also like to know whether the hemoglobin content of the blood taken from the vein corresponded with that taken from the peripheral circulation.

The protrusion of the eyes reported suggests an affinity with exophthal-

mic goiter; on the other hand, the cyanosis recalls Raynaud's disease. I will not at this time pursue this thought further than to ask whether there is any possibility of the condition being spasmodic? The relief afforded by venesection would seem to point in that direction. The effect of nitrites might help to answer this query.

As Dr. Osler has referred to polycythemia in general I may relate a case of high erythrocyte count varying from eight to nine millions in the person of a physician who had made a mistaken diagnosis in his own case of interstitial nephritis on account of persistent polyuria. The heart was somewhat large and weak, and what I assumed to be a hemic murmur was present. There was, however, no enlargement of the spleen; no cyanosis; no excess of hemoglobin; on the contrary, the hemoglobin was only 65. The erythrocytes showed no change other than diminution in size. Leukocytes were normal in number and kind. The patient improved on the administration of iron, the red cells diminishing in number to about five and a half millions, and increasing in size. The hemoglobin rose to nearly 90.

The case seems, therefore, one of chloroanemia, and its only relation to the present discussion is the unusual fact of polycythemia.

DR. OSLER: As to the protrusion of the eyes; when I first saw the case it suggested exophthalmic goiter. His wife assured me that he had the condition for many years, and there was no enlargement of the gland. Headache has been a most frequent feature and in one case reported it has been relieved by the use of sodium nitrite.

DR. CABOT: As to the spectroscopic examination inquired about by Dr. Cohen, we used it in one of the cases and found the ordinary oxyhemoglobin bands. The hemoglobin was in excess.

DR. SHATTUCK: As to Dr. Stockton's question as to the nature of the relief afforded by venesection, I would say it was simply a feeling of increased comfort—a lessening of the distress.

POST-TYPHOID SEPSIS.

By FRANCIS DELAFIELD, M.D.,
OF NEW YORK.

Typhoid fever, as a disease, regularly lasts for four weeks, with periods of improvement at the end of the second and third weeks. These periods of improvement may be permanent, so that we have two-week, three-week, and four-week typhoids. If, after the expiration of these periods, the patient has fever it is usually not typhoid fever, unless there is a true relapse. A true relapse is a fresh attack of typhoid fever.

When a person suffers from a bacterial infection, this does not by itself make a disease. The disease is the complex product of the bacterial infection and the various morbid changes that go with it. To make up a true typhoid there go together the bacterial infection and the intestinal lesions. When these have run their course other things may happen, but they are not typhoid fever.

There may be inflammation of the gall-bladder, of the urinary bladder, of connective tissue—all due to infection with typhoid bacilli, but they are not typhoid fever.

In the same way, after typhoid fever there are fevers which may be due to typhoid bacilli, or to other infections, but they are not typhoid fever.

It is to these post-typhoid fevers that I wish to call attention.

We must first distinguish the true relapses, which are really fresh attacks of typhoid fever with the regular features of the original attack. The interval between the end of the original attack and the beginning of the relapse is from three to twenty-five days. The relapse lasts from seven to thirty-nine days. A single relapse is of ordinary occurrence; a second relapse is comparatively rare.

Chart I. shows a typhoid of four weeks' duration, an interval of seven days' duration, and a relapse of seventeen days' duration.

Chart II. shows a typhoid of eighteen days' duration, a first interval of twenty-three days, a first relapse of seven days, a second interval of eleven days, and a second relapse of seven days' duration.

Now, if we turn to the post-typhoid fevers, which are not typhoid fever, we distinguish:

1. The ordinary moderate rises of temperature, only lasting for a few hours, occurring within three weeks after the end of a typhoid fever. These short fevers would not be recognized at all unless the temperature was systematically taken, for they are not attended with any symptoms, and do no harm. The only important thing about them is to understand that they are not of importance.

2. The post-typhoid fevers which are of real importance and last for one or more weeks, but yet do not make the patient very ill, and are not fatal.

In 1898 Dr. Da Costa published a clinical lecture on "Post-typhoid Fever," in which he gave a good descriptionof these fevers and recognized clearly that in order to bring them to an end it is necessary not only to give the patients solid food, but to get them out of bed.

If one looks for this form of fever it is found to occur quite frequently. I have seen it after typhoid fevers of two, three, or four weeks' duration. The rise of temperature is continuous with the typhoid temperature, or there may be an interval of several days of normal temperature, and then the post-typhoid fever begins.

The morning temperatures run pretty near the normal, the afternoon temperatures run from 100° to 103°, with occasional jumps to 105° or 107°. With the very high temperatures there may be chills.

With this fever there is no delirium or sleeplessness; the tongue is moist and clean; there is no eruption, no tympanites, no diarrhea. The patients are hungry. If they are not fed they may have rather alarming attacks of heart failure. As long as the patients are kept in bed and on a fluid diet there is no particular limit to the duration of the fever, but yet in the end they get well.

Chart III. is of a three-weeks' typhoid. After the typhoid

there was an intermission of two days. After that the afternoon temperature ran from 100° to 103° until the thirty-eighth day. The patient was fed on the twenty-third day, taken out of bed on the thirty-third day, and discharged on the fifty-third day. After the twenty-third day he gained steadily in strength and had no bad symptoms except the fever.

Chart IV. is of a four-weeks' typhoid, followed by an intermission of seven days, then the afternoon temperatures ran at 100°, with a rise to 105° on the forty-fifth day, of 102° on the forty-seventh day, and of 101° on the fifty-first day. The temperature fell to the normal on the fifty-third day, and the patient was discharged on the fifty-seventh day. He was fed on the twenty-eighth day and taken out of bed on the thirty-fourth day. He gained flesh and strength steadily after the thirty-fourth day. On the fifty-second day the hemoglobin was 94 per cent., the red cells 5,280,000.

Chart V. is of a three-weeks' typhoid. There was no intermission, but a steady afternoon temperature of 101° until the forty-third day. The patient was fed on the twenty-second day, taken out of bed on the thirtieth day, and discharged on the forty-ninth day. On the thirty-fourth day he was feeling perfectly well and rapidly gaining flesh and strength. On the forty-first day the hemoglobin was 70 per cent., the red cells 4,722,000.

Chart VI. is of a two-weeks' typhoid with a positive Widal reaction. There was an intermission of six days. Then on the twenty-first day the temperature ran up to 105°, on the twenty-second and twenty-third days to 107°. With these rises of temperature there were chills and sweating, with some prostration. There was no thrombosis of the veins. On the twenty-fourth day he was doing well, on the twenty-eighth day he was out of bed, and on the forty-sixth day he was discharged.

It is very interesting in these patients, if they are fed and taken out of bed, to see how they steadily gain flesh and strength in spite of the fever.

3. Much more important than these mild fevers are the severe and long-continued post-typhoid fevers, which may terminate fatally. They occur regularly after well-marked and severe typhoid fevers which run their full four-weeks' course. The septic fever is

FIG. 5

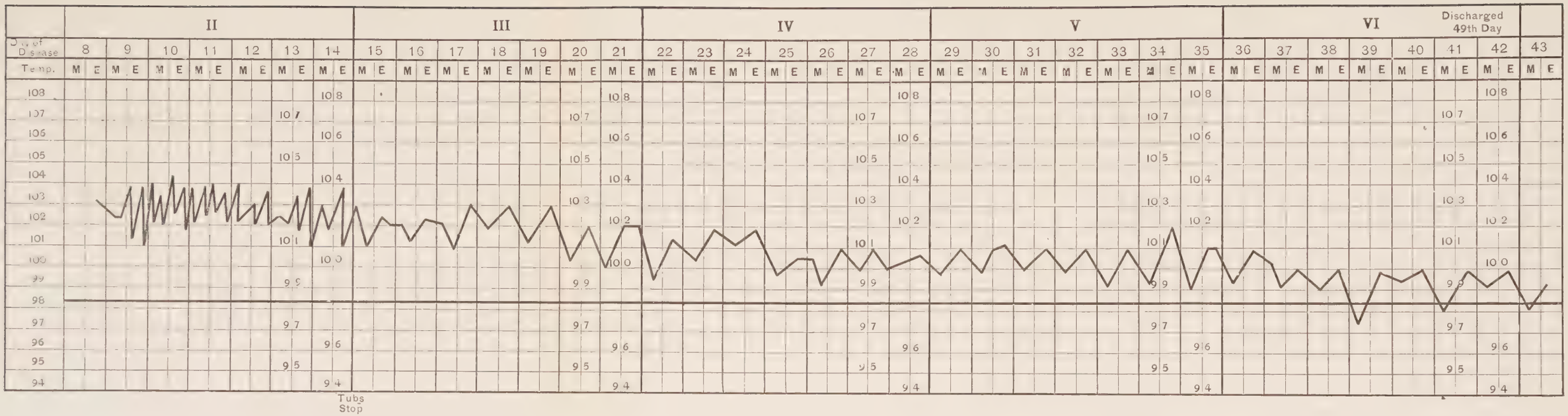

II
III
IV
V
VI
Discharged 49th Day
Day of Disease
Temp.
Tubs Stop

FIG. 6

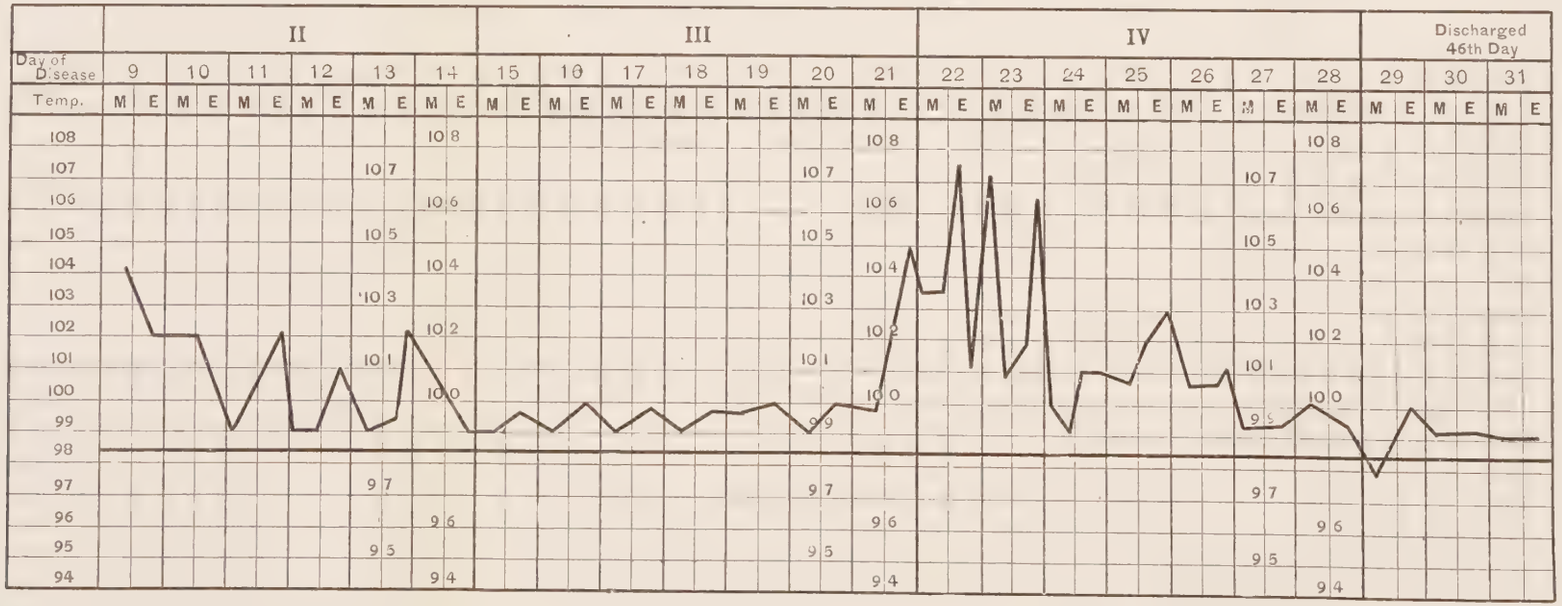

II
III
IV
Discharged 46th Day
Day of Disease
Temp.

FIG. 3

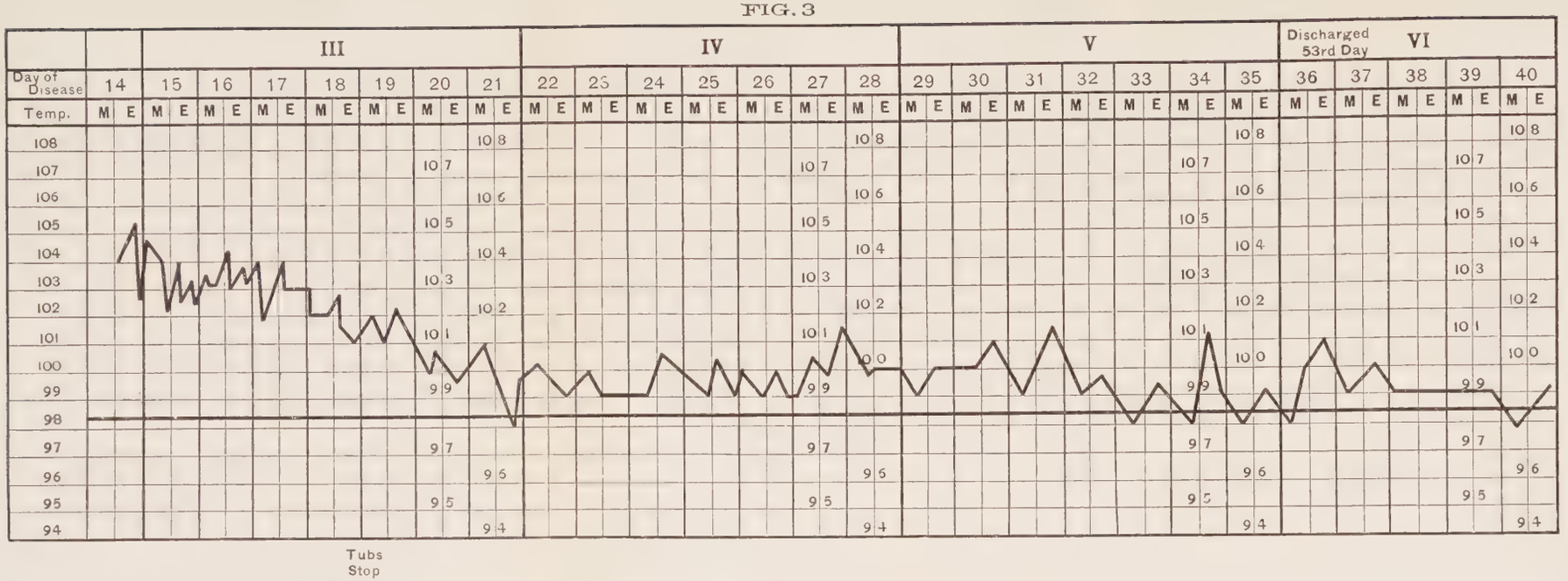
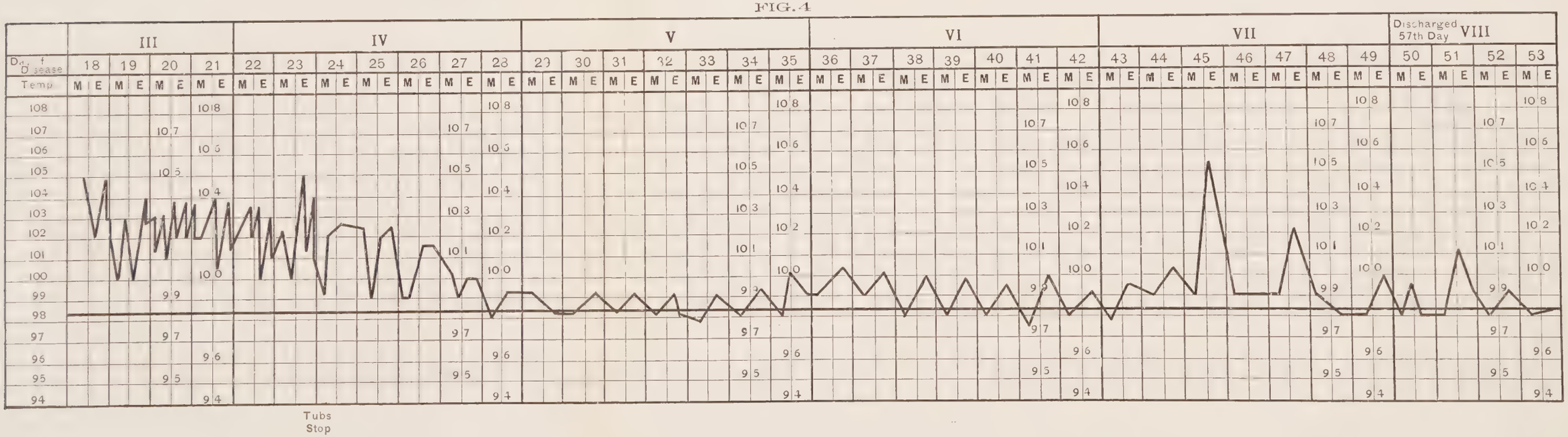

III
IV
V
Discharged 53rd Day
VI
Day of Disease
Temp.
Tubs Stop

FIG. 4


III
IV
V
VI
VII
Discharged 57th Day
VIII
Day of Disease
Temp
Tubs Stop

continuous with the typhoid fever. Sometimes it even overlaps it, so that both fevers seem to be going on together in the fourth or fifth week.

The morning temperatures run about 100° and the afternoon temperatures about 103°. In many cases there are sudden jumps of temperature up to 105°, 106°, or 107°. These jumps occur in the course of the regular fever, or there are intervals of one or more days with nearly normal temperatures, and then the sudden rise. With these sudden rises of temperature there are often chills.

It is noticeable that the septic temperature is not controlled by baths, as in typhoid temperature, but runs up and down quite without reference to them.

The patients look septic and not in the typhoid state. The mind is often dull and apathetic, but they are not actively delirious. The tongue is dry ; there may be nausea and vomiting, and yet there is some desire for food. There is a rapid loss of flesh and strength, as in ordinary sepsis, so that the condition may become alarming. In some of the cases there is thrombosis of one or both femoral veins. If the patients are insufficiently fed and kept in bed they are very apt to die.

In the autopsies of the fatal cases which I have made, the intestinal lesions were healed, and there seemed to be no cause of death but sepsis and starvation.

Some of the patients improve on food alone, but in most of them there is no real convalescence until they are taken out of bed. Then they gain flesh and strength, even while the fever continues.

It must be confessed that it requires a good deal of courage to take out of bed a patient who is apparently dying ; but I am fully convinced that the only way of saving the life of the bad cases is to feed them and take them out of bed.

Chart VII. is that of a woman who had a pretty severe typhoid, favorably affected by tubbing, which ran its course in four weeks. On the twenty-ninth day she had a chill and then went on with temperatures between 99° and 104° up to the forty-ninth day. She kept on in the septic condition, steadily getting worse and weaker until the forty-sixth day, then she was given solid food, and after that the improvement was rapid.

Chart VIII. is that of a man with a well-marked typhoid, which

ran its course in four weeks. He was hungry on the twenty-sixth day. After this he ran along with temperatures between 100° and 103° until the fifty-ninth day, but yet he was not so very sick. He was fed on the fortieth day and taken out of bed on the forty-sixth day. Between the fiftieth and the seventy-eighth day he gained twenty pounds in weight.

Chart IX. is that of a man who had a severe typhoid until the eighteenth day, when he was evidently less poisoned. On the twenty-fifth day he had a chill, the temperature ran up to 107°, and he looked septic. There was no thrombosis of the veins; the white blood cells were 6900. Apparently the septic poison was overlapping the typhoid. He also had nausea and vomiting. He went on after this with irregular afternoon temperatures, often up to 104°, not at all controlled by tubbing until the forty-third day, when the tubs were stopped; they had been of absolutely no use after the twenty-first day.

On the forty-fifth day he was fed. On the forty-seventh day, although he was so ill and weak it seemed doubtful if he would recover, he was taken out of bed. After this the temperatures were very irregular, running up to 106° and down to normal. There was no real improvement until the fifty-first day. After that he improved steadily, although there was thrombosis of the left femoral vein on the fifty-ninth day and of the right femoral vein on the sixth day. There was no more fever after the sixty-eighth day. He gained thirty pounds in weight between the sixty-ninth and the one hundred and fifth day.

Chart X. This is perhaps the most interesting case of the series. The man had a pretty severe typhoid, but began to improve on the twenty-fifth day and was fed on the twenty-sixth day. He continued to improve, although the temperatures were up to 104° in the afternoon, until the thirty-third day. Then he had a severe chill; the temperature ran up to 106°; there was thrombosis of the left femoral vein, and he looked distinctly septic. After this he failed steadily, lost flesh and strength, and seemed likely to die.

On the forty-third day, although with much misgiving, for it seemed like handling a dying man, I got him out of bed. The chart shows that during the following week the temperature did not go over 101°, and his general improvement was most satisfac-

tory. After this he got steadily better, although he had irregular rises of temperature and a complicated orchitis on the seventy-sixth day. He was discharged on the eighty-third day.

Chart XI. This man went on with an ordinary typhoid until the third week, when the temperature began to rise. In the fourth week he had high septic temperatures with chills, and on the twenty-fifth day thrombosis of the left femoral vein. On the thirty-eighth day he had thrombosis of the right femoral vein. He went on with irregular septic temperatures until the fifty-ninth day, but yet his general condition improved after the thirty-ninth day. He was fed on the thirty-ninth day, taken out of bed on the forty-third day, and discharged on the seventy-eighth day.

Chart XII. This man had a typhoid fever lasting for four weeks, then there was an intermission of three days. Then there was a true relapse, which lasted for ten days. During the relapse he began to become septic and developed thrombosis of the right femoral vein on the thirty-eighth day. In the seventh, eighth, and ninth weeks the rises of temperature were curious, with intervals of one, two, three, and four days. There were no malarial organisms in the blood. He was fed on the thirty-seventh day, taken out of bed on the fifty-second day, and discharged on the seventy-fourth day.

The impression I have received from the study of such cases is that in the end of a typhoid fever there may come in a new infection which resembles a streptococcus infection. This infection may be mild or severe. With care I think it can be usually distinguished from the typhoid infection.

The point of practical importance is that this infection calls for a different management from that of typhoid fever. The best results are obtained if the patients are fed and taken out of bed.

It is to be noted that this post-typhoid infection occurs in private practice as well as in hospitals.

In the charts the arrows at the bottom indicate chills.

The charts as seen here are reduced from larger charts prepared for me by Dr. Rolfe Floyd.

DISCUSSION.

Dr. Koplik: In children it is very common to see the temperature run very much as in Charts 2, 3, 4, and sometimes 6, for a short period. It is very common after the fourth week for the patient (when I say children, I mean from four to twelve years of age) to run a slight temperature for a day or two, which then falls; or it falls to the normal and then gradually rises to 100 or 100.5 and stays there for some time. If the child has been sick with typhoid fever four or five weeks, the temperature having fallen to the normal, I begin to feed these patients, in spite of the occasional crises of temperature, and sometimes even get them out of bed. These children are emaciated and some physicians continue to starve them. I formerly saw the results of this treatment when I came back from my vacation and went through the wards. The children would be still running a slight temperature and the very careful house physician would be continuing the starvation method. On getting these patients out of bed and feeding them the temperature would subside. I have found this common in children and have always acted on the principles laid down by Dr. Delafield. The condition seemed to me to be one either of inanition from lack of nutrition or a reinfection from the intestine independent of typhoid fever.

Dr. Peabody: Whatever the interpretation of the facts may be, I am inclined to agree with Dr. Delafield as to the conditions which he has described. Unquestionably these cases do occur and the results following the feeding of these patients and getting them out of bed are good.

It would be interesting if we could have bacteriologic cultures from the blood of these cases. In one case, in a woman who had had a double femoral thrombosis, and to whom I was giving solid food, I had a culture taken from the blood and got nothing but a pure culture of the typhoid bacillus, although clinically the condition was distinct sepsis. She soon got out of bed, and prior to that we had been able to take her out-of-doors. It seems to me there should be some definite rule for the beginning of solid food in typhoid fever. My own rule for twenty years has been simply to follow the dictates of the patient's appetite. As soon as the patient is hungry I draw the inference that the stomach is in a condition to do some work. It is important, of course, to distinguish between real hunger and the desire of a patient to eat in order to get well. One must eliminate that possibility. As to what is the best solid food to begin with, I have for some years myself been inclined to favor the very hard-boiled egg, twenty minutes or a half hour, so that a few touches are sufficient to reduce the yolk almost to a powder. That exposes a large surface for the contact of the gastric juice and renders it very digestible. I am often surprised to find that prejudice exists in favor of the soft-boiled egg, or even a raw one. The first thing that happens in the process of digestion is coagulation, and if you can save the

stomach this work of coagulation by doing it on the stove you accomplish that much. After that you can pass on to meat and later to farinaceous food. These patients with post-typhoid fever improve immediately on the administration of solid food, and they fail to improve without it.

DR. ROBINSON: As far as my observation goes, I believe that there are a certain number of cases in which this is not true. There is a certain period after typhoid fever when the temperature is irregular and there are unaccountable rises which we find difficult to explain. Sometimes we feel that it is due to the fact that patients are receiving too little nourishment. We give them food, but find that the temperature does not drop. My belief is simply this, and, of course, there is nothing new about it, that most practitioners, where the patient has been on a limited diet, lose sight of the fact that there may be an indication for some purgative treatment. There is fear of perforation, and I believe that it is an unnecessary fear. I believe that if we used mild purgatives we would have less of these unexplained rises in temperature.

A CASE OF PULSATING SEROUS PLEURAL EFFUSION.

By ALEXANDER McPHEDRAN, M B.,
OF TORONTO.

Mrs. J., a widow, aged fifty years. She was of neurotic temperament and had suffered serious reverses in fortune. She had never been robust, but her only serious illness was diphtheria, followed by marked paralysis, three years ago. She made a complete recovery. Late last autumn (1902) she began to lose strength. She had laryngitis from which she recovered, but a moderate cough which she had had for some time persisted. There were no bacilli of tuberculosis in the sputum. Her temperature was normal and her pulse ranged from 80 to 100 per minute.

On Christmas Day she had slight chills for a few hours. A few days later pleural effusion was discovered in the left side. There had been no disturbance of temperature or pulse. As the fluid was not absorbed, the aspirator was used, and forty ounces of blood-stained fluid was removed. Before its removal there was well-marked pulsation over the effusion round to the spine. The pulsation disappeared as soon as most of the fluid was removed.

The effusion recurred, and as soon as a moderate quantity was present the pulsation returned. The second aspiration was also blood-stained, but subsequent ones were clear serous fluid. The fluid was removed in all five times, a trocar and canula being used on the last two occasions. From the canula the fluid flowed in pulsating jets that were easily seen across a long room.

When I saw the patient with her physician, Dr. Musgrave, in March last she was quite prostrate. The upper border of the effusion was at the fifth rib in the midaxilla. The heart was in its normal position and its impulse quite easily seen and felt. As

she lay on her back there was marked pulsation in the axilla in the sixth and seventh intercostal spaces, but not at the back. On turning her on her right side the pulsation disappeared in the axilla and became marked in the back below the lower end of the scapula. On turning her on her back again it reappeared in the axilla and disappeared at the back. The position of the heart did not change with the change of position of the patient.

Her temperature was normal, her pulse small and weak. She died three weeks later without a repetition of aspiration being required. Request for an autopsy was not acceded to.

It is not my purpose to discuss the various theories that have been advanced to explain the occurrence of pulsation in pleural effusion. Pulsation in purulent cases is a rare phenomenon, but in serous ones it is extremely infrequent, only a few undoubted cases having been reported.

In the case herewith reported it is to be noted that the heart was not displaced, even when the effusion was quite abundant, rising as high as the fourth rib. This is accounted for probably by firm adhesion of the pericardium to the thoracic wall. It is quite possible, also, that the left lung was retracted so as not to intervene between the pericardium and the chest wall round to the back. Then if the pericardium were also adherent to the heart, or at least lay in close contact with it, the impulse of the heart would be communicated directly to the pleural fluid and through it conveyed to the chest wall. The intercostal muscles, in common with the general musculature, were quite atonic and offered little resistance to the impulse being transmitted through to the surface.

It is probable that the mechanism of pulsation in pleural effusion is not constant. The theories advanced by various writers may each be correct for their individual cases. It is also to be noted that pulsation similar to that of pulsating pleurisy may occur without the presence of any fluid in the pleura or the existence of an aneurysm. This is shown by the remarkable case of Edwards, in which the pulsation was both diffuse and expansible, and yet neither pleural effusion or aneurysm were found at the autopsy.[1] Dr. Lafleur, of Montreal, also communicates a similar unpublished case.

[1] American Journal of the Medical Sciences, October, 1902.

DISCUSSION.

Dr. Henry: The condition which most closely simulates pulsating empyema necessitatis is a thoracic aneurism which is "pointing" at some portion of the chest wall and has leaked into the pleural sac so as to fill that cavity and give rise to the signs of pleurisy with effusion. A case is now under my observation at the Philadelphia Hospital which either belongs to this category or to that of pulsating pleurisy (necessitatis) with hemorrhagic effusion. I am inclined to regard it as of the latter variety, because the blood withdrawn on repeated punctures has never escaped in jets.

A CASE OF MASSIVE HEMORRHAGIC INFARCTION OF THE LUNG DUE TO PULMONARY END-ARTERITIS AND THROMBOSIS.

By A. McPHEDRAN, M.B.,

AND

J. J. MACKENZIE, B.A., M.B.,
OF TORONTO.

The question of the relative frequency of thrombosis of the branches of the pulmonary artery, as compared with embolism, as a cause of hemorrhagic infarction of the lungs is one about which opinions have differed widely; the reason for this difference of opinion has been due, partly to fundamental differences in the explanation of the pathology of the hemorrhagic infarctions of the lung, but partly also to uncertainty as to the explanation of the origin of the plugs found in the artery to the infarcted area. The tendency of several of the more recent writers on the subject has been to give more prominence to thrombotic processes in the production of pulmonary infarction than formerly. Grawitz, notably, has insisted upon primary thrombosis, but there seems no doubt that he has somewhat exaggerated the frequency of thrombosis as compared with embolism. Newton Pitt has also insisted upon the comparative frequency of the occurrence of primary thrombosis, but in his paper he seems to depend far too much upon evidence from the gross appearance of the plug and the negative evidence of a source for the embolus in support of his view to render it tenable. In many cases only a microscopic study of the arterial plug would show whether it formed *in situ*, due to disease of the vessel wall, or whether it was a small embolus, and the fact that a source for this embolus could not be demonstrated is no evidence against the embolic origin. Welch, in discussing

Pitt's view in the article in Clifford Allbutt's *System of Medicine*, while admitting that fatty degeneration or sclerosis of the intima are by no means rare, and that primary thrombosis of the pulmonary artery may be more common than the text-books would lead us to suppose, yet maintains that the majority of the plugs of the pulmonary artery are embolic in origin.

In view of the discussions which have arisen within the past few years upon this question of thrombosis of the pulmonary artery, it may not be without interest to describe a case which we have had an opportunity of studying, in which there was an undoubted primary thrombosis of the smaller branches of the pulmonary artery, and in which the thrombotic process was so gradual in its development as to illustrate very clearly many points in regard to the formation of hemorrhagic infarctions of the lung tissue.

The history of the case was as follows:

William H., aged fifty-five years, a street laborer, doing heavy work, and subject to much exposure. He was admitted to the Toronto General Hospital on December 3, 1902, complaining of pain in the lower part of the right thorax, weakness, troublesome cough, with dark bloody expectoration, some dyspnea, especially when lying down. There was also considerable edema of the lower extremities. He was not clear mentally, and a definite history could not be obtained, but so far as could be learned he had been ailing for some weeks, at least with some shortness of breath and edema of the legs. He had lived roughly, but had never used much alcohol. He had smoked heavily. There was no history of lues or gonorrhea.

His present illness began evidently rather gradually, as there is no evidence of an acute onset. He was a large man and very well nourished. He was somewhat dazed, so that he had to be watched to prevent him rising and going about the ward. He was considerably jaundiced; the temperature was about 100° F.; the pulse from 85 to 100 per minute, and respiration about 24; the appetite was poor; there was no complaint of thirst; the bowels moved daily, but there was no diarrhea. The legs and feet were markedly edematous. The breathing was somewhat labored, so that he had more comfort sitting up than lying down.

The circulation was weak, the pulse being small and soft; the

heart sounds feeble and its impulse not perceptible; the left border of the heart extended one inch to the left of the nipple line, and the right border to the right margin of the sternum. There was no murmur; a weak one would have been obscured by the loud respiratory sounds. The arteries were only moderately sclerosed. In the axillary part of the base of the right lung the breathing was tubular and very weak; occasional friction sounds were audible; the resonance was defective and the fremitus was decidedly increased; there were many moist râles and rhonchi in all parts of the lung, being especially numerous in the right base. The liver was very large, its lower margin being three and one-half inches below the costal margin in the mammary line; its surface was smooth, and it was tender on deep pressure. The spleen could not be felt. The abdomen was not distended, and no fluid could be detected in it. The sputum was viscid, dark red, and contained many red blood cells and encapsulated diplococci. The blood contained 14,600 leukocytes per cubic millimeter. The urine was high-colored and acid; its specific gravity was 1012, and it contained some bile pigment. There was no albumin or casts. During the following week his condition grew gradually worse. The temperature ranged from 97° F. to 101° F. for five days, and then remained at normal, falling to 97° F. at times. The respiration was not quickened until the eighth day, the day of his death. The sputum was at times very abundant and consisted almost wholly of dark blood. The jaundice deepened considerably, and pain in the right side persisted. The consolidation of the right lung gradually extended upward to the fourth rib in front and to the third dorsal spine behind, with impaired resonance above these points. He died on the eighth day after admission, the symptoms being much worse for the last two days.

Autopsy fourteen hours after death. The subject is fairly well nourished; skin and conjunctiva markedly jaundiced; a few petechial hemorrhages on the upper arms; pupils unequal; edema of the legs extending up to the knees; a few pigmented scars about the ankles.

Subcutaneous fat deep yellow in color; peritoneum is normal in appearance, and the cavity contains a small amount of bile-stained fluid; the omentum is small, its veins are congested, and the fat is

a deep yellow in color. The height of the diaphragm in the mammary line on the right side is at the upper border of the seventh rib, on the left side the upper border of the sixth rib. The right lobe of the liver extends four fingers' breadth below the costal margin.

On opening the thoracic cavity the right lung is found to extend three fingers' breadth to the left of the middle line; the right pleural cavity contains a large amount of clear, blood-stained fluid mixed with flakes of fibrin, and the visceral pleura is covered with fibrin flakes, especially at the margins of the lobes; the lobes are adherent owing to the fibrinous deposit. The visceral pleura is intensely congested, and through it the lung appears deep red or in many places almost black in color. On section the upper lobe is found to be crepitant and emphysematous throughout an area including the apex and free margin; the middle portion of the upper lobe is markedly edematous, and the lower and posterior third is consolidated, the consolidated area being reddish-black in color and of an even firmness, not granular, with the exception of a small area on the pleural surface, which is softened; this softened area has no odor; between the area of consolidation and the edematous portion of the upper lobe is a band about a centimeter in width, which is distinctly gray in color. The middle lobe is entirely airless and consolidated and deep reddish-black in color. The lower lobe is also almost entirely consolidated and of the same deep red-black hue; there is in this a narrow zone at the upper border which is crepitant and of a more normal color. The right bronchus and its branches are deeply congested and contain blood-stained fluid mixed with air.

The left pleural cavity contains a small amount of bile-stained fluid, and the pleural surfaces are free from adhesions. The left lung is emphysematous, and on section shows hypostatic congestion and edema of the dependent portions; at one point at the lower posterior margin of the lower lobe there is a small area of consolidation, reddish-black in color and resembling a hemorrhagic infarction, but not sharply marked off from the area of hypostasis. The bronchus to the left lung and its branches are deeply congested and contain a blood-stained froth.

The pulmonary artery just above the valves shows one or two small areas of pale-yellowish discoloration, but the endothelial

surface is unbroken and the intima apparently only slightly thickened; a few similar areas can be seen on the larger branches of the artery. The branch to the lower right lobe is completely occluded by a thrombus, which projects into the right artery as a pinkish-yellow, nodular mass; this clot is mottled red and white as far as it can be traced: it is friable and over a good part of its course in the larger branches can be separated cleanly from the arterial wall, although here and there it is apparently adherent. All the branches to the middle lobe are occluded by similar clots, which project into the main branches as nodular outgrowths; in the upper lobe the branch to the infarcted area is similarly occluded. The pulmonary veins show nothing special.

The pericardium contains a small amount of bile-stained fluid. The serous membrane is normal with the exception of a slight roughening over the right auricle and some epivasal fibrotic spots.

The heart is very large, weighing 755 grams. Its muscle has a greenish tint and is firm, but does not show any fibrosis.

The coronary arteries are somewhat sclerotic.

The left auricle is distended with dark clot mixed with gas-bubbles; the left ventricle is also distended with clot; the chamber is dilated and its walls are somewhat hypertrophied.

The right auricle is distended with dark clot mixed with gas-bubbles; the right ventricle is also filled with clot, mostly settling clot stained with bile; the right chambers are dilated and the ventricular wall is hypertrophied.

The mitral valves show slight fibrosis and the orifice measures 13.5 cm. across; the aortic valves are somewhat fibrosed along their free margins; the tricuspid valves are yellowish in places and slightly thickened; the tricuspid orifice measures 14.9 cm.; the pulmonary valves are normal; the artery measures 10 cm. across its face at the level of the valves. The aorta shows atheroma of the ascending portion and the arch, with a few calcareous plaques; the atheromatous change is much more marked in the descending aorta, and all the abdominal branches show extensive arteriosclerosis.

The liver weighs 1567 grams and is normal in shape; the surface is slightly roughened by the presence of small depressed scars in the capsule; scattered over the surface are seen about

twenty small yellow spots about 2 mm. in diameter surrounded by a hyperemic zone, which is about 1 mm. in thickness; on section the central yellow portion seems structureless, but of firm, elastic consistency, not caseous, and it can be scooped out entire; the same hyperemic zone completely surrounds the section. The liver on section shows a few of these yellow spots scattered through its substance; the lobular markings are well defined, the central zone being congested, the portal zone swollen and fatty; the whole liver is bile-stained.

The gall-bladder contains dark, tar-like bile; the hepatic, cystic, and common ducts are free from gross obstruction or stenosis.

The only condition worthy of note in the stomach is a marked dilatation, the greater curvature lying below the umbilicus; the mucosa is atrophic, shows passive congestion, and contains bubbles of gas. The duodenal mucosa is edematous and contains gas bubbles.

The spleen is slightly enlarged, its capsule showing patchy perisplenitis. On section the organ is pale and markedly fibrous.

The kidneys are of normal size, surface smooth, capsule stripping readily, stellate veins congested; the parenchyma dense, the cortex thinner than normal, and showing a number of small retention cysts, especially the left kidney.

The remaining abdominal organs showed nothing of special interest. The brain and spinal cord were not examined.

Microscopic Study of the Tissues. Lung. The upper lobe of the right lung in the infarcted area shows all the typical characters of a hemorrhagic infarct; at the inner margin of the infarct the alveoli are filled with polymorphonuclear leukocytes, and this zone passes insensibly over into the edematous area. With this exception and a condition of emphysema, the upper lobe appears practically normal.

The microscopic picture of the middle lobe is one of complete infarction, but the extent to which death of the cells of the alveolar wall has taken place varies a good deal from area to area. The general appearance is one of a very recent infarction.

In the lower lobe the condition is much more interesting and varied in character; with the exception of a small band of crepitant tissue along the upper border the whole lobe is engorged with blood and quite solid; the hemorrhagic color varies a good deal, in some

places being fairly bright red, in others almost black. Under the microscope a large portion shows the ordinary appearance of an infarction: alveoli filled with blood and the nuclei of the pulmonary tissues, staining very badly or not staining at all; in some places, however, there is very distinct evidence of increased fibrous tissue in the alveolar wall, and this becomes more marked as we pass to the base of the lung; here the appearance of the lung is that of a chronic pneumonia, the alveolar walls enormously thickened and in some alveoli undoubted polypoid ingrowths of new connective tissue. This area of chronic pneumonia occupies the lower third of the lower lobe, and here the microscopic evidences of infarction are not so marked, there being not so marked an engorgement and no necrotic change in the cells.

In this portion there is further evidence of the chronic inflammatory change in the bronchioles; in some of these the wall is thickened and the ciliated epithelium is replaced by a low, stratified, squamous epithelium; this condition is, however, not general, only an occasional tube showing it.

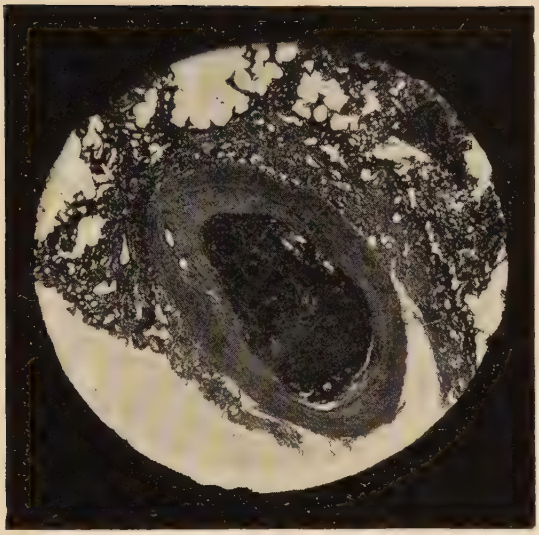
In the vascular apparatus to this lobe one sees a most interesting condition; as pointed out in the description of the gross changes, the pulmonary artery shows a few areas of sclerotic change; on microscopic examination of these plaques it is seen that in the main vessel and its larger branches this is not very prominent; there is an evident increase in the subendothelial layer, but this is not very great, and it is not until we come to study the condition of the smaller branches, those the size of a small quill and smaller, that we get an extensive endarteritis. In these vessels the intima is irregularly thickened, in many places being three and four times the thickness of the media; the endarteritic change is usually eccentric in distribution and at the thickest point it frequently shows vascularization. These sclerosed vessels are everywhere thrombosed and the thrombus varies in its character from point to point of the vessel; in some places it is completely organized, so completely organized that when stained by Weigert's elastin stain fine new elastic fibers can be found in the connective tissue in the vessel lumen; in other places organization is just beginning, and in many others no trace of organization can be found. The most complete organization is found in those

vessels about the size of a match; the smallest branches, although showing endarteritis, are simply filled with red clot; in those branches a little larger than the ones in which complete replacement of the thrombus by connective tissue has taken place, one finds thrombus with beginning organization, and in still larger the thrombus is present, but no connective tissue formation can be seen.

It is evident from the microscopic picture that the thrombosis began in the vessels of a certain caliber and that it slowly progressed toward the larger ones, and that only with involvement of those of a fairly large size did the circulatory embarrassment become so great as to lead to infarction. This point, however, will be discussed more fully when considering the general explanation of the condition in this lung. The microscopic characters of the vascular changes are illustrated by Figs. 1, 2, 3, and 4.

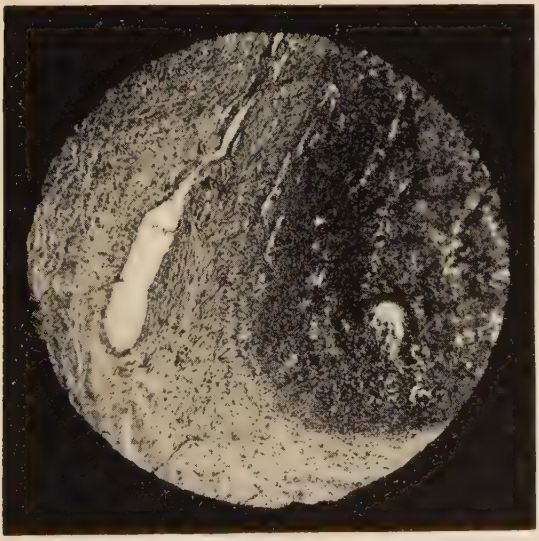
The liver upon microscopic examination is seen to be in a state of passive congestion, the capillaries of the central zone of the lobule being distended with blood, the trabeculæ of liver cells somewhat atrophied and pigmented; in the peripheral portion of the lobule the cells are somewhat infiltrated with fat; the bile capillaries are everywhere filled with bile and the cells contain droplets of bile. The interlobular bile ducts do not contain bile, but some of them seem to contain a mucus-like secretion. The sections of the yellow areas, mentioned above, show a central necrotic mass surrounded by an area of young fibrous tissue and fibroblasts mixed with large numbers of small round cells. The fibrous tissue is cutting into the surrounding lobules, the vessels of which are intensely congested. In many places about these structures, which are undoubtedly miliary gummata, one can trace the fibroblasts along the capillaries into the neighboring tissue. The scars on the surface run down into the liver substance and evidently represent healed gummata. Outside these areas there is no hepatitis. A few small colonies of a bacillus were found in certain of the liver sections, but there is no evidence of reaction of the tissue about them, so that they are evidently postmortem in development. No cultures were made, but the organism resembles bacillus aerogenes capsulatus in form, and this taken with the presence of gas in the auricles and in the intestinal mucosa,

FIG. 1.



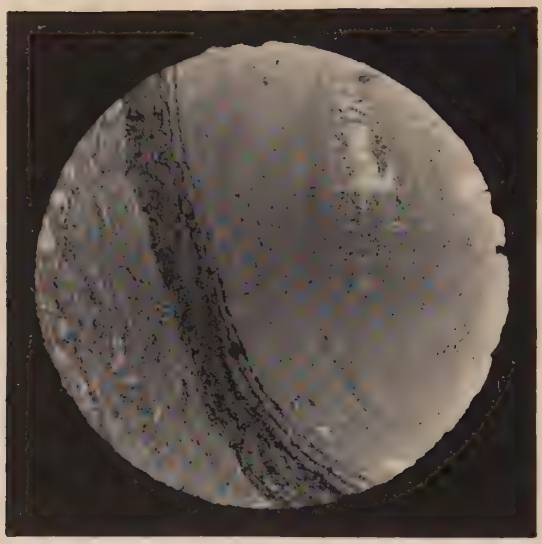
Small branch of the pulmonary artery, showing endarteritis and thrombosis. Note the vascularization of the intima.

FIG. 2.



Portion of media; thickened and vascularized intima; beginning organization of thrombus. Zeiss a a, projection ocular 2.

FIG. 3.



Small branch of right pulmonary stained with Weigert's elastin stain. Note the thickened intima. Zeiss a a, projection ocular 2.

FIG. 4.

Small branch of right pulmonary. Stained with Weigert's elastin stain. Low-power photograph.

makes it probable that there was an agonal or postmortem infection with an organism of this group.

The variation in the amount of organization which had taken place in the thrombi, the distribution of the new connective tissue, and the distribution of the endarteritis point most conclusively to a very gradual filling up of the pulmonary artery by the thrombus, and, taken with the history of the case, to a gradual infarction of the right lung. Welch, in his article in Allbutt's *System of Medicine*, vol. vi. p. 208, quotes a case reported by Blachez, in which the thrombosis and resulting infarction presented the same gradual development; we have not had an opportunity of examining the original paper, but from the reference it would seem that the cases were somewhat similar. With the exception of Blachez's case, we have not been able to find in the literature an exactly similar case.

The question which arises at once in regard to our case is: How are we to interpret the changes met with in the vessels of the lung and in the lung tissue? Although the history of the patient is negative in regard to syphilis, there is no doubt as to the syphilitic character of the changes in the liver; these are undoubtedly miliary gummata. Are we, then, to regard the pulmonary and vascular conditions as due to syphilitic disease? This is a question which is by no means easy to answer. There was in this lung certainly nothing of the nature of the gummatous change which is commonly the characteristic finding in syphilitic disease of the lung of the adult, and yet, when we consider the manifold changes of a fibrotic character which may result from syphilis, and especially when we remember the characteristic predilection of the virus for the vascular apparatus, we are in doubt as to whether we should class the condition in this case as one due to syphilis or not. The pulmonary changes which are to be interpreted as a chronic inflammatory process are confined to the right lower lobe, and consist in a thickening of the alveolar wall not unlike that of a brown induration, and the resemblance to this condition is heightened by the presence of hemosiderin pigment in the tissue. In addition to these there are the changes in the bronchioles of the nature of a chronic bronchitis. Aufrecht, in Nothnagel's *Encyclopædia*, discusses at length the characters of these atypical syphilitic pneumonias, quoting especially Rollett, Schnitzler, and Hiller, and from his descriptions

there would seem to be a resemblance between our case and the diffuse non-gummatous types, but the difficulty that we meet with is that the hemorrhagic infarction of the right lung has masked the other pathological conditions which preceded it. It seems more than probable, however, that in this case we have had to do with a diffuse syphilitic inflammation of the lower lobe of the right lung involving also the smaller branches of the pulmonary artery to that lobe.

The extent to which the organization of the thrombi has taken place is of some interest in relation to the question of the production of the hemorrhagic infarction of the lung. The thrombosis of the smaller branches did not sufficiently interfere with the circulation to produce infarction, and the nutrition of the tissue was such that new connective tissue could form in the arterial lumen; but the endarteritis and resulting thrombosis lead to a gradually progressing thrombosis toward the heart, and when this had proceeded sufficiently far, interference with the circulation took place, and the resulting massive infarction occurred. Although the clinical history pointed to an involvement of the base of the right lung as the earliest condition, the microscopic examination of the lung shows undoubtedly that the oldest infarcted area is that in the upper lobe, because here we see evidence of the softening of the infarct and an acute pneumonic inflammation of the tissue surrounding the infarct.

Of considerable clinical interest was the marked jaundice which was a feature of the case. We do not think that the syphilitic hepatitis was of sufficiently extensive a character to account for it, but are more inclined to think that it was a result of the infarction and was due to the very large amount of blood destruction which was going on in the infarcted lung, with, as a result, the passage of an abnormally large amount of dissolved hemoglobin to the liver. In fact, the jaundice had a similar origin to that seen in experiment animals as the result of the administration of hemolytic poisons or of hemolytic sera.

REPORT OF A CASE OF DECAPSULATION OF THE KIDNEY (EDEBOHLS' OPERATION) FOR CHRONIC PARENCHYMATOUS NEPHRITIS.

By JAMES TYSON, M.D.,
PROFESSOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

CHARLES H. FRAZIER, M.D.,
PROFESSOR OF CLINICAL SURGERY, UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE UNIVERSITY HOSPITAL.

That the therapeutics of chronic Bright's disease has been practically at a standstill for some years is painfully recognized by all practising physicians. Therefore the announcement of Dr. George M. Edebohls that he had instituted a new operation for the cure of this disease is of absorbing interest to all, and especially to those to whom the disease has been the subject of special study. Edebohls' paper, published in the *New York Medical Record* for December 21, 1901, containing a report of nineteen cases, of which eight were seemingly well at the date of publication of the paper, strongly impressed the writers. A natural conservatism restrained us, however, from taking advantage of numerous opportunities to apply the operation until the case about to be reported presented itself, evidently past all relief by the usual medicinal treatment. Even then the operation was not performed until a final trial had been made of those measures under the direct superintendence of the senior writer. The case is as follows:

Fannie W., aged nine years, born in Philadelphia, was admitted to the Hospital of the University of Pennsylvania, November 11, 1902.

She had scarlet fever when four years of age (five years before admission). During and immediately after the fever she had no dropsy. One year after, however (four years before admission),

she presented symptoms of acute nephritis, including albuminuria and general anasarca, which responded promptly to treatment at a hospital in New York City. Subsequent to this she had five relapses, for which she was treated at different hospitals in this city, with more or less complete recovery so far as objective symptoms were concerned, each attack requiring more time to overcome it. The last relapse set in about two weeks before she consulted Dr. Tyson, when she had general anasarca, with ascites, albuminuria, and casts. The edema was extreme. The face was so swollen that the eyes were almost closed, and the abdomen was enormously distended with fluid. She was sent to the University Hospital, where the examination was completed. Her temperature was 99° F., the pulse 126, the breathing rate 28. There did not appear to be much fluid in the pleural cavities, and the lungs were normal. The cardiac action was feeble; there were no murmurs, but the second aortic sound was accentuated. The liver outline was difficult to obtain because of the ascites, but seemed normal. The urine on admission was acid in reaction, specific gravity 1016, and contained one-half its volume of albumin; there was no sugar. The microscope found pale granular, medium granular, and dark granular casts; also free fatty renal cells. The quantity secreted during the first twenty-four hours was twenty ounces. The blood examination found 45 per cent. of hemoglobin, with 6,320,000 red corpuscles—probably an erroneous estimation.

The patient was immediately put to bed, on a milk diet, and ordered cardiac tonics, with eliminative treatment by saline cathartics and hot-packs. The remedies acted as they were expected to, and some relief to symptoms followed, but it was incomplete. On November 18th paracentesis abdominis was done, but on account of a defective instrument only six ounces of a clear fluid were withdrawn.

Under treatment the urine secreted was increased at one time to thirty ounces, and there was some diminution in the anasarca, but it was only temporary. Paracentesis was done repeatedly, with the removal of a clear spring-water liquid, and so persistently did the ascites return that some concurrent cirrhosis of the liver was suspected. She became very much reduced in strength, and after all medical treatment had been unavailing and it seemed she must

die unless something else was done, she was transferred to the wards of Dr. Frazier, January 11, 1903, for operation, which was done January 13th, a large accumulation of abdominal fluid being first removed. She was so weak that it was thought unwise to operate on both kidneys at once, and accordingly at the first operation the right only was decapsulated.

The immediate effect of the operation was truly astonishing. In the first twenty-four hours after it was done the quantity of urine secreted was only 21½ ounces, but in the second twenty-four hours it reached 42½, in the third 72½, in the fourth 102, in the fifth 63 ounces, and in the sixth 60 ounces. In ten days after the operation ascites and anasarca had entirely disappeared and continue absent up to the present time Before the operation the volume of albumin was one-half; by the middle of February it had fallen to one-tenth the volume of urine tested. For three weeks prior to the second operation the patient was allowed to be up and about, after which the albumin largely increased, becoming almost as large as when she came under observation. The casts did not disappear, but continued quite numerous up to the date of the second operation.

On March 14th, just two months after the first operation, the left kidney was decapsulated by Dr. Frazier. Surgically the case progressed rapidly to healing of the wound.

After the second operation, the urine, of course, did not increase as it did after the first, as there was no edema to drain off, but ranged from 30 to 60 ounces in the twenty-four hours. Four days after the operation the albumin measured one-sixth volume, with hyaline and pale granular casts. About April 2d the patient was allowed to get up, but almost immediately the albumin increased to one-half volume, and she was promptly returned to bed (April 6th). Since that time there has not been any marked reduction in the quantity of albumin; in fact, it has remained about the same. The urine has, however, been secreted freely, and the casts have been mainly hyaline and slightly granular. The patient has again been allowed to get up, and has remained free from dropsy and is, in fact, the picture of health. It cannot be said that there has been a cure, and it is impossible to say that there will be. On the other hand, there can be no doubt the

patient's life has been saved, and apart from the urinary evidences she is seemingly in perfect health.

SURGICAL REMARKS BY DR. FRAZIER.

I. Decapsulation of the Right Kidney. On January 13, 1903, under nitrous oxide-ether anesthetization, the right kidney was exposed by oblique incision parallel to the last rib. The kidney was larger than normal, its contour irregular, with depressions here and there at the site of pre-existing infarcts, perhaps; its surface was mottled with purplish blotches irregularly distributed. The fatty capsule was stripped without any difficulty, and a longitudinal incision through the true capsule was made from one pole to another. The true capsule, which seemed unusually thin, was stripped from the kidney surface back to the pelvis and trimmed away with scissors. The hemorrhage following this procedure was not very free, but sufficient to warrant the introduction of drainage upon closing the wound.

II. Immediate Effects of the Operation. 1. *As to the Anasarca.* It was a source of regret to me that a photograph of the patient was not taken before and after the operation; such an illustration would have demonstrated more forcibly than words can depict the—I might almost say magic—way in which the anasarca vanished. The child was edematous from head to foot, and not only were the cellular tissues involved, but the peritoneal cavity was distended to its utmost with ascitic fluid. One week after the operation upon only one kidney the anasarca had disappeared.

2. *As to the Quantity of the Urine.* As the anasarca disappeared so rapidly, one would expect to find that the amount of urine eliminated per diem was very much greater after the operation than before, as the following daily record shows:

First twenty-four hours	. . . . .	21½	ounces.
Second " "	. . . . .	42½	"
Third " "	. . . . .	72½	"
Fourth " "	. . . . .	102	"
Fifth " "	. . . . .	63	"
Sixth " "	. . . . .	60	"
	6)	362½	"
		60+	"

Thus in six days a total of 362 ounces of urine were voided, an average of 60 ounces per diem, the maximum, 102 ounces, having

been attained on the fourth day. From this time on the total daily quantity gradually decreased to an amount varying from 35 to 40 ounces.

3. *As to the Quality of the Urine.* The qualitative changes in the urine after the operation have, on the whole, been disappointing; not so much because the improvement was not rapid, but because it was not progressive and because at no time was the urine entirely normal. We find that from the date of the operation, January 13th to February 20th, a period of about six weeks, the albumin gradually diminished from more than one-third by bulk to one-tenth by bulk, and that casts while diminished in numbers, never entirely disappeared. More than half of this time the patient was confined to bed, as it did not seem wise or prudent to allow her to assume the erect posture until the kidney was firmly anchored in place by adhesions.

III. Decapsulation of the Left Kidney. On March 14th decapsulation of the left kidney was practised. The operative procedure differed in no way from that carried out upon the right kidney.

Immediate Results of the Second Operation. The patient recovered from the immediate effects of the operation without any untoward symptoms, save that for the first twenty-four hours there was rather persistent vomiting. Inasmuch as there was no anasarca before the second operation, and as the daily amount of urine eliminated was approximately normal, the polyuria which followed the first operation was not looked for after the second. The patient voided during the first seven days 8, 29, 26, 26, 38, 50, and 48 ounces, respectively.

As to the quality of the urine the history of the effects of the first operation rather repeated itself. Two weeks after the operation the albumin had diminished until there was just a trace and there were only a few hyaline casts; and, as after the first operation, when the patient was allowed to get up and was allowed the freedom of the ward the albumin and casts again appeared.

IV. Ultimate Results of the Two Operations. As the patient was transferred back to the service of Dr. Tyson after she had fully convalesced from the operative intervention, I shall leave to Dr. Tyson the account and record of this case from that

time to the present. Though the patient was desperately sick when the first operation was performed, she at no time gave us the slightest concern, either during or after the operation. Both operative procedures were borne unusually well.

I might refer, in passing, to the observations that were made upon the blood during the convalescence. Repeated examinations showed that from the date of the first operation to that of the second there was a continued leukocytosis, on an average of about 16,000. It is difficult to explain satisfactorily this phenomenon. Had the wound been infected it would not have been surprising, although even then in well-drained wounds such a disturbance of the leukocytes is not at all usual. But even after the wound had closed the leukocytosis continued. Hypothetically one might ascribe it to the reparative or regenerative processes that might have been going on for some time, even after the external wound had closed, about the kidney—the formation of granulation tissue and the organization of this into connective tissue. I have seen the same phenomenon exhibited during the repair of a simple fracture, and it seems to me quite reasonable to draw an analogy between these two conditions—both of them subcutaneous wounds undergoing repair—the one of bone, the other of soft tissues.

V. The Operative Technic. This phase of the subject calls for little or no comment. The method of exposure differs in no way from that to be employed when proposing to carry out any of the other operations upon the kidney. Any of the conditions which interfere with the exposure of the kidney within the wound or its deliverance without the wound—such as great length and obliquity of the twelfth rib or an additional floating rib, a contracted iliocostal space, a kidney with but little mobility, or a very firmly adherent capsule—naturally make the operation more difficult. If after the kidney has been reached the operator finds it impossible to move it from its position behind the ribs, the proper procedure, according to Edebohls, is to incise the capsule at any portion of the surface that can be reached, to seize the edges of the capsule wound with forceps, and to complete the separation of the capsule proper from the kidney in the depths of the wound.

The amount of bleeding that follows the removal of the capsule is a very clear indication for the insertion of drainage; a strand of

gauze or a few strands of silkworm-gut should be introduced when the wound is to be closed, and allowed to remain for twenty-four to forty-eight hours.

As to the advisability of operating upon one or upon both kidneys at the same time, I feel that this is a matter which must be left to the judgment of the surgeon, whose decision will vary according to the peculiarities of the individual case. If the patient's condition is such as to offer but little prospect of recovery from any operative interference, I believe, on the whole, the mortality will be lower if but one kidney is attacked at a time. Not only is prolonged anesthesia a grave consideration in subjects of chronic nephritis, but the shock attending such a formidable attack on two kidneys must be considerably greater than that upon one. To be sure, the abstraction of blood from the kidney that necessarily follows the decortication in a measure counteracts to some extent the congestive effect of the anesthesia. In the case which I operated upon the patient's condition did not seem to me to warrant an attempt to decapsulate both kidneys at one time; her condition was one so unfit for surgical intervention that my surgical judgment rebelled against undertaking anything which would add to the immediate risks of the operation, providing this could be done without precluding the possibility of subsequent operation and ultimate recovery. The subsequent course of events seemed to justify this opinion. The patient's condition improved so materially after the first operation that I approached the second operation with no special concern.

Before speaking of the indications for operation or its results, I wish to refer to a series of experiments, involving a study of changes noted in the renal and perirenal tissues of dogs after decapsulation, undertaken by Dr. Harold A. Johnson, of San Francisco (*Annals of Surgery*, April, 1903). These observations were made upon fifteen dogs at times varying from two days to three and one-half months. Dr. Johnson found that the first manifestation of this procedure was a thin exudate appearing on the free surface of the kidney, which with the remains of the inner layer gradually becomes a fibrous investment, resembling macroscopically the normal capsule in that it strips readily and that with the passage of time it becomes more and more firm. Microscopic

examination reveals the fact that it is in some cases thicker and in others thinner than the original capsule, the former generally being true. There is sometimes an infiltration of the round cells and a proliferation of the intertubular connective tissue of the cortex without affecting the glomeruli. The dogs in which these changes were noted remained perfectly well as far as could be shown by their appetite, strength, and playfulness. Lastly, and of the most importance, in no case was there any considerable anastomosis between the renal and perirenal bloodvessels. In one case the decapsulation of one kidney and ligation of the renal artery of the other were performed at the same time, with the idea of provoking increased activity in the circulation of the decapsulated kidney. The increase in the vascular supply was all made up, however, by an increase in the size of the renal artery and vein and not through any peripheral anastomosis.

As Johnson has pointed out, the difficulty in the way of drawing any inference from these observations as to the curative and palliative effect of this operation in cases of nephritis is the impossibility of provoking experimental interstitial nephritis in dogs.

To the objections that have already been advanced against Edebohls' conclusions others are suggested by the result of Johnson's experimental observations. According to Edebohls' conclusion, the improvement is due to the formation of new bloodvessels, which anastomose with those of the kidney. Johnson showed that "the added demands made on the circulation of one kidney caused by the removal of the other, either with or without decapsulation of the first, does not in the dog produce an increased vascularity of the perirenal tissue." Furthermore, there was in no case of the experimental series any considerable anastomosis between the renal and perirenal bloodvessels, and so far this phenomenon has not been confirmed by evidence from the autopsy table.

This would naturally lead us up to the question of the *rationale* of the operation. If, as has been above stated, there is no proof that a peripheral collateral circulation is established between the renal and perirenal structures, the theory upon which Edebohls bases the improvements following his operation is without foundation. Unless the improvement is due, as Israel and Pousson have suggested, to the relief of tension from splitting the capsule of the

kidney, we are at a loss to explain the unquestioned improvement which is known to follow this simple operative procedure.

From clinical observations we have seen improvement immediately follow the operation. Theoretically, should we expect this improvement to be continuous until recovery finally ensues? The answer to this question would seem to be "No." Both from our knowledge of the histologic changes that take place in the tissues that have been subjected to such manipulations as are described, and the results of Johnson's experimental work already outlined, lead us to but one conclusion, viz., that in course of time, through the organization of the granulation tissue into connective tissue, the kidney will be again surrounded by a capsule fibrous in character and probably several times thicker than the original one; so that, whether viewed from the immediate or from the ultimate effects, with our present knowledge we must regard the operation as irrational.

VI. Prognosis. This must be considered from several points of view: first, as to the immediate dangers of the operation, and, secondly, as to the benefits to be enjoyed by the survivors.

1. *Mortality.* As Edebohls' experience is very much greater than any other individual observer, I will quote statistics from his experience, which includes a series of fifty-one cases. Of these seven died within seventeen days. The operative mortality might, therefore, be said to be approximately 14 per cent. As to the number of recoveries or improvements, seven, or about 14 per cent., are quoted as having survived the operation on an average of one year and eight months, some only two months, one as long as eight years. Twenty-two patients, or 43 per cent., have been improving for periods varying from two to fifteen months after the operation. None of them as yet may be classified as cured. One patient had recurrence, and nine, or 17.5 per cent., were cured and have remained cured for periods varying from twenty-one months to ten years. To sum up in a few words the results of Edebohls' experience, one could say that there is one chance in seven of an operative death; there is the same chance of enjoying little or no relief without prolongation of life; there are two chances in five of experiencing improvement which may terminate in recovery, and one in six of permanent recovery.

2. *Indications.* It is a very difficult matter for a surgeon to undertake to formulate in a precise manner any indications from the performance of this operation. It must still be regarded as in the empirical stage, and he must be content for the present to confess that he is ignorant as to the manner in which the operation exercises any beneficial results upon the altered kidney structure. If there is any organic lesion which the surgeon would regard as a *contraindication* to operative intervention, it is chronic nephritis.

The routine careful analyses of urine prior to operations are made solely for the purpose of determining the functional activity and health of the kidney substance, with a view toward determining whether or not the proposed operation may not be contraindicated, or whether our opinion as to the time, necessity, or character of the operation may not be somewhat modified. This very class of patients which we, as surgeons, consider so undesirable is now presented to us as a class in which (it is alleged) benefits may be derived by surgical intervention ; and not only this, but of this objectionable class none but the most hopeless is likely to come into the surgeon's hands. When, therefore, as at the present time, the surgeon is asked to discuss the indications for an operation upon the desperate cases of a rather desperate disease, the problem is not one of any breadth of scope. I take it for granted that neither the physician nor the surgeon of to-day would be willing even to discuss the question of operation in all cases of Bright's disease, but only in those in which the prognosis as to prolongation of life for any length of time is very unfavorable.

Personally, I have in the past been skeptical in my attitude toward this operation, and with some reluctance decided to operate upon the patient the subject of this report. The improvement, however, in this case was so striking and so unquestionably and directly attributable to the operation, that I have been forced to conclude that one cannot justifiably disregard such results obtained in a patient so desperately sick, and without the slightest prospects of recovery. In the future, therefore, I should not hesitate to perform this operation in a patient in which all attempts at alleviating the condition by every means, other than operation, had failed, and in which the patient was daily losing ground and death was imminent, provided it was reasonable to assume that the patient

would survive the immediate effects of the operation. I am opposed to the practice of operating upon cases simply because death seems imminent and every other mode of treatment has failed. I believe it to be the duty of the surgeon to exercise his judgment as to the justifiability of operation, even in these apparently hopeless cases, and to refrain from operating indiscriminately in perfectly forlorn cases, quieting his conscience with the familiar "I will give the patient his only chance."

DISCUSSION.

DR. MCPHEDRAN: An interesting case occurred in the Children's Hospital of Toronto under the care of Dr. A. Primrose. A boy, aged ten years, who had anasarca and ascites for six months, had been tapped seven times before coming into the hospital. On admission there was distention of the abdomen and general anasarca. The urine was of low specific gravity, only fourteen ounces in twenty-four hours was passed; it contained 1.6 per cent. of albumin. There was an abundance of casts of all kinds. His condition was very grave. He was tapped and 180 ounces of fluid removed. The next day Dr. Primrose exposed the right kidney and split the capsule. A few days later, the urine had increased to forty ounces in six hours, and the albumin had fallen to 0.8 per cent. He did not continue to improve, and six weeks later, his condition being unsatisfactory, the left kidney was operated on, a complete decapsulation being done. The condition after the operation was grave, and at the end of a week he contracted pneumonia and was very ill. He improved again, the urine increased in quantity, the albumin fell to a mere trace, and the casts became fewer. The general edema and anasarca also disappeared, and he left the hospital in good condition. He was seen a few weeks ago, and he was in a vigorous, healthy state. The result was very satisfactory, but whether wholly due to the operation may be open to question.

The original theory in regard to the matter, suggested by Reginald Harrison, of London, to whom is due the credit of having first operated on such cases, was that the operation relieved tension of the kidney, but in this case the kidneys were not tense.

DR. CUTLER: I have had three cases—two in adults and one in a child, aged eleven years. The first one was in a desperate condition when the operation was performed. He improved; his urine increased in quantity, and the albumin diminished in the same ratio as has been spoken of by Dr. Tyson, and there was a great increase in the amount of fat excreted in the urine after operation. About the third month later he commenced to dete-

riorate and died. At operation the diagnosis had been confirmed by cutting out a portion of the kidney for examination by Dr. Wright. The post-mortem showed the kidney to be in the same condition it had been before, and there had been complete regeneration of each of the capsules.

The next case was that of a woman of middle age whose condition improved, and during the eight or nine months that I followed its progress it was uninterrupted. The albumin diminished and the casts disappeared almost completely. She felt so well that she returned to her duties as a servant, and when I last saw her, sometime in the early winter, she appeared perfectly well, and said she felt so, though albumin in small trace and a few casts were present in the urine.

The third case was one of post-carbuncular nephritis of five years duration. He was in a desperate condition, and the parents planned to have something done. He improved from the first. There was the same increase of urine and diminution of albumin and increase in fat as in the other cases. At the end of a year he was apparently in good health. He had spent the winter mostly in the house, and had not gone to school. He felt so well, however, that he resented the restraint that was upon him, and said he was perfectly well. He has increased in weight, strength and height, and certainly looks to be in perfect health.

A NOTE ON AUTOLYSIS IN LOBAR AND UNRESOLVED PNEUMONIA.

By SIMON FLEXNER, M D.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF PENNSYLVANIA.

(From the Pathologic Laboratory of the University of Pennsylvania.)

The interest which has been revived in the study of the self-digestion of organs and exudates by the appearance of Jacoby's and Conradi's studies upon autolysis has been followed by a series of important observations upon this phenomenon, both as affecting physiologic and pathologic processes. Some years ago I studied sections of the lungs in unresolved pneumonia, with a view of discovering the existence of some essential distinction in the pathologic process as compared with that to be observed in an ordinary lobar pneumonia, which might account for the different manner in which the two sets of processes tend to conduct themselves. The outcome of this study was unimportant and consisted merely in my becoming strongly impressed with a fact which had been emphasized before, namely, that the exudate in the alveoli in unresolved pneumonia is often dense and hyaline and poor in cells.

With the appearance of Jacoby's and Conradi's papers on autolysis, it occurred to me that possibly the explanation of the failure of the exudate in unresolved pneumonia to be absorbed readily might lie in an imperfection of the autolytic processes taking place in the inflamed lung, and, acting upon this suggestion, I began immediately to study autolysis of the lung in pneumonia.

My opportunities for obtaining specimens of the lungs, the seat of pneumonia, were excellent. By utilizing the pathologic material from the Philadelphia Hospital, the Hospital of the University of Pennsylvania, and the Pennsylvania Hospital, I succeeded within

two years in securing not only many specimens of typical lobar pneumonia in various stages of the disease, but also some ten or twelve examples of unresolved pneumonia.

That organs protected from decomposition tend to undergo solution by a process of self-digestion was first accurately shown by Salkowsky in 1882; and this process of autolysis has now been studied from many different sides. The nature and distribution of the active ferments have been investigated, the question of their multiplicity and specificity attacked, their influence upon the coagulability of the blood upon bacterial life, upon cellular degeneration under physiologic conditions and upon the resolution and absorption of pathologic products, formations, and exudates studied. As a result of these studies, we have already learned that in the intracellular ferments causing autolysis we possess a most important and potent series of agents which come into play under both physiologic and pathologic conditions.

All that is required to convince one's self of the phenomenon of autolysis is to place a portion of the liver or other organ or a quantity of exudate under conditions protected from decomposition and maintained at blood heat, when digestion will proceed. Care must be exercised to avoid using means of preventing putrefaction that may injure unduly the ferments. Two kinds of autolysis are now distinguished: (*a*) antiseptic, in which it proceeds under chloroform or toluol, and (*b*) aseptic, in which the organs are exposed in a sterile condition. Manifestly only the first method is applicable to certain pathologic products in which bacteria are present. As a result of this self-digestion the coagulable albumins are converted into non-coagulable proteid and certain by-products, among them leucin and tyrosin, make their appearance.

Differences are noticeable in the readiness with which autolysis of organs takes place under different pathologic conditions. Jacoby found that liver autolysis was much accelerated in animals poisoned with phosphorus; and I have made some tentative experiments upon the rapidity with which organs from infected and non-infected human beings undergo this change.

Every pathologist has been impressed with the remarkable softness presented by the liver, spleen, kidneys, and other organs in persons who have succumbed to typhoid fever, peritonitis, septi-

cemia, etc. This softness has nothing to do with putrefaction, and I think it reasonably certain that it is the result of autolytic processes which may have begun to operate even before death. The changes through which the acutely swollen spleen goes, such as is met with in typhoid fever, illustrate very well the manner of action of these ferments. The diffluent quality of the spleen in this disease quickly develops outside the body, and it can be shown to be independent of the postmortem growth, either of the typhoid bacilli or putrefactive bacilli. It is not a very unusual experience to observe a moderately firm spleen outside the body become soft and semifluid in a few hours; and I find that, reduced to a pulp and placed under toluol-water, the same change takes place.

In view of the resemblance of the hepatic lesions of advanced phosphorus poisoning to those of the liver in acute yellow atrophy and the frequency with which the latter obscure disease supervenes upon acute infections, and, further, in view of the close agreement of the chemical products of degeneration of liver tissue in yellow atrophy with those of autolysis of the liver, the question arises whether the hepatic lesions in acute atrophy may not be the result of active autolytic processes set up by some agent that is as yet unknown.

The alterations in structure and consistence of muscle occurring in certain acute diseases (such as the so-called Zenker's degeneration which appears in typhoid fever) have features in common with changes noted in autolysis. The softening and preparation for absorption of infarcted areas in the brain, kidney, spleen, and other organs are also attributable to the action of intracellular ferments; and a similar form of softening occurs, if imperfectly, in malignant tumors, notably in carcinoma and in syphilis, where ferment action is possibly accelerated through the use of drugs, of which potassium iodid is the most efficient in use.

On the other hand, not all dead tissues are subject to this digestive liquefaction and absorption. Tuberculous foci, though degenerated, are remarkably persistent, and, as Prudden has shown, undergo softening probably only when certain bacteria invade secondarily the necrotic areas. It is of importance in this connection to recall that streptococci, which in themselves are not energetic tissue dissolvers, bring about softening and cavity formation

in tuberculous foci; and the question as to whether their action is a direct one through products of their growth or an indirect one by causing an increase in autolytic ferments is pertinent, but not as yet to be answered.

Fresh pus obtained, let us say, from an empyema or fresh sputum, kept under toluol at the body temperature, becomes fluid, and a creamy layer collects upon the surface. The cells and nuclei disappear, and there appears in the fluid, as Naunyn first ascertained in 1865, various disintegration products, among which are leucin, tyrosin, xanthin, guanidin, etc. Pus which thus undergoes digestion is capable of dissolving fibrin and even portions of organs independent of the action of bacteria. From this the conclusion can be drawn that pus, or really the leukocytes of pus, possess active digestive properties, a fact which the manner of abscess formation and the removal by leukocytes of necrotic and other kinds of tissue renders easily comprehensible. Many years ago Weigert attempted to explain, by assuming the operation of a peculiar poison which prevented fibrin-formation, the absence of fibrin from abscesses, etc., in which the fibrin factors must have originally been present. It is much more probable that what happens is a digestive transformation of fibrinogen or of fibrin at the moment of its formation, by the ferments of the pus cell.

Broadly speaking, exudates and necrotic tissue are removed in two ways: (1) by absorption and (2) by organization. In the first mode disintegration and solution of the cells, etc., with the exception of the fat and certain other elements, such as pigment, take place, and an emulsion results well adapted for entrance into the lymphatics. In the second new vessels develop and invade the exudate or necrotic tissue, and by supplying a fresh set of leukocytes to dispose of the offending material it is finally removed. From what has already been said, the first series of changes will readily be recognized as caused by autolysis, but the operation of the same cause is not so apparent in the second series. And yet, the two series would seem to be essentially the same. In the one the original material contains ferments of a kind and in a quantity sufficient to bring about the transformation which is necessary before absorption can take place: in the second the ferments, being originally insufficient, are renewed by fresh leukocytes which emi-

grate from the vessels, load themselves with débris, and, finally, accomplish its entire removal.

There is little doubt that in many pathologic conditions the leukocyte is the essential agent in bringing about absorption, and what is required to accomplish this end is not living leukocytes so much as large numbers of these cells, since autolysis proceeds independently of the vitality as such of the cells. The fate of pathologic formations is dependent in large part on the number of leukocytes present within them.

The different behavior of a caseous and croupous pneumonia, the facility with which the one and the difficulty with which the other undergoes resolution, is to be ascribed probably in large part to the absence in measure of leukocytes from the tuberculous process and their presence in enormous numbers in the acute inflammatory condition. Other examples illustrating the importance of leukocytes in promoting autolysis and absorption might be given.

Friedrich Müller first studied autolysis of the lung in croupous pneumonia, and described in detail its occurrence and the chemical products, among which are lysin, leucin, tyrosin, purin bases, and phosphoric acid of the digestive process. I have found that it is in the stage of gray hepatization that autolysis takes place quickly and perfectly, while in the stage of red hepatization it is very imperfect—a fact that can, I think, be attributed to the small number of pus cells present in the latter condition ; but if the lung in unresolved pneumonia is exposed to conditions favoring autolysis, the process is slow and incomplete as compared with what takes place in gray hepatization. In gray hepatization autolysis after death is a mark of the tendency during life of the exudate to become absorbed; in unresolved pneumonia the absence or reduction of autolysis is equally an indication of the future fate of the exudate, namely, during life to undergo organization.

The study of the histology of the lung in various stages of the process of organization emphasizes one pathologic condition, the import of which appears great in view of our present knowledge of autolysis ; the exudate in unresolved pneumonia is fibrinous rather than cellular, and many of the alveoli of the lung are filled with dense hyaline, fibrinous masses. All attempts to explain upon ordinary etiologic grounds the peculiar changes or absence of

changes in unresolved pneumonia have failed ; and evidently the peculiarity of the process is to be sought in other causes. I am, therefore, inclined to view unresolved pneumonia as an acute lobar pneumonia in which the inflammatory exudate, either because of some disproportion between the leukocytes and other constituents, or other causes as yet unknown, failing to autolyze perfectly, cannot be absorbed, and hence undergoes organization.

DISCUSSION.

DR. JACOBI: Just one remark from a clinical point of view. There is a rapid absorption in cases of lobar pneumonia when it is uncomplicated. This lobar pneumonia is a surface affection. Those not readily absorbed are complicated with interstitial connective tissue inflammation (interstitial pneumonia, peribronchitis). The cases that do not get well are not so much cases of lobar pneumonia as of interstitial pneumonia, and the cases we see in after-life of retraction of the thorax, mainly above or below the right clavicle, with prolonged expiration, bronchophony, and dulness, mostly without râles, and which are liable to be mistaken for chronic tuberculosis, are of that type.

DR. MELTZER: I should like to ask Dr. Flexner if he knows of any studies as to the antiseptic properties of the blood in pneumonia. I think it is a question whether it is an autolysis or an antiseptic action of the blood.

DR. FLEXNER: I know of no such studies as Dr. Meltzer has spoken of. The only point is this, that eventually the exudate is gotten rid of, even in the unresolved pneumonias, but there it is delayed. The method of removal is the same, but it takes place more slowly, because new vessels are required apparently to carry the ferments in sufficient quantity to remove the substances. I have studied in the last two years perhaps a dozen examples of unresolved pneumonia, and I think that it is not the exudate that one finds in the ordinary pneumonias that go on to resolution. This condition is not found only in the unresolved forms, but if the lungs in the early stages of lobar pneumonia are examined in the same way there is a similar imperfection in the autolysis and the same delay. The exudate is very poor in leukocytes, and where the leukocytes are diminished there is delayed autolysis.

A FURTHER REPORT ON THE STUDY OF BACTERIAL CELLS.

By VICTOR C. VAUGHAN, M.D.,
OF ANN ARBOR, MICH.

Last year I made a somewhat lengthy report upon work done in my laboratory under the head of "A Study of Bacterial Cells." I do not propose this year to inflict upon the Association a detailed account of the work that has been done during the last twelve months, but I have thought that it might be of interest to give a very brief statement of the progress of this work.

Dr. Wheeler has been engaged in a study of the chemistry of the bacillus typhosus. The material used was obtained by growing the organism on the large tanks described to you two years ago. This material after being taken from the tanks was put in Soxhlet extractors and freed from fat by means of ether and alcohol, after which it was ground into a fine powder and passed through a fifty-mesh sieve, by means of which a uniform standard powder free from traces of agar was obtained. The first thing done was to ascertain whether the substances split off from this germ substance by means of dilute acid were altered by the strength of acid employed. Two ten-gram samples of the powdered germ substance were extracted, one with $\frac{1}{10}$ per cent. sulphuric acid and the other with 1 per cent.; extractions being made in the cold, on a water-bath, at 110° and at 120° C. The extracts were then precipitated with three volumes of 95 per cent. alcohol, the precipitate filtered out, washed, and dried. It was found that a definite cleavage takes place and is effected by either the weaker or stronger acid. In both cases the total amount of split product was practically one gram, or 10 per cent. of the powdered germ substance. It is interesting to note in this connection

that two years ago while working with the colon bacillus I obtained in one experiment, from fifty grams of the germ substance, five grams of the material split off with dilute sulphuric acid and precipitated with alcohol.

The split products obtained by both dilutions of acid, as well as the final residue, were found to be toxic for guinea-pigs, though not so highly poisonous as the germ powder itself. It is possible that the split products are not single substances, but that they consist largely of some inert body with which the real toxin is mixed. All these acid extracts give the xanthoproteic test, and those above 100° give the biuret test also. With all, the Millon test is doubtful. It should be stated that these side chains split off from the bacterial cell by means of dilute acid are not only toxic to guinea-pigs, but when injected into these animals in small doses repeatedly produce in the blood serum of the treated animals a substance which gives the Widal test. This indicates that the action of these split substances is specific, inasmuch as the blood serum of animals treated with them agglutinates the typhoid bacillus and fails to agglutinate other micro-organisms. Ultimate analyses of some of these split products were made and will be reported when the work is completed. In addition to the study of the split products, Dr. Wheeler has continued her investigations and has obtained certain hexon bases and amido acids, an account of which will be given in a subsequent publication.

Dr. Gelston has studied the physiologic action of the cellular substance of the typhoid bacillus and also of the split products obtained by Dr. Wheeler. His conclusions may be briefly stated as follows :

1. The toxicity of the typhoid cell substance is inversely proportional to the virulence of the culture.

(*a*) The minimum fatal dose of the powdered germ substance varies from 1 part to 15,000 parts of body weight to 1 part to 35,000 parts of body weight in guinea-pigs.

2. The toxin of the typhoid cell is relatively an unstable substance. Its instability is evidently much greater than that of the colon toxin.

(*a*) The action of moist heat upon the toxicity of the typhoid cell seems to be peculiar. Heating the cell substance in the pres-

ence of moisture for thirty minutes at from 75° to 100° markedly decreases its poisonous properties, while heating to a temperature of 110° certainly increases the toxicity of the cell substance.

3. By the action of hydrolytic agents it is possible to split off from the typhoid cell a poisonous group or side chain, which probably corresponds to or is identical with the specific toxin of the typhoid germ.

4. Prolonged exposure of the cell substance to water, although there is no appreciable amount of toxin extracted, renders it more highly poisonous.

5. Extraction of the cell substance with glycerin, either diluted or concentrated, removes a small amount of toxin.

6. The subcutaneous injection of one-tenth the minimum lethal dose, given intraperitoneally, has no effect upon guinea-pigs beyond causing a slight induration at the point of inoculation, and animals thus treated are found to be immune to living cultures. Animals similarly treated with the cell substance that has been heated to 110° are not protected against living cultures.

7. The blood serum of a horse immunized with sterilized typhoid culture has but slight protective action against the intracellular toxin.

8. Animals treated with the cell substance and with the split products obtained by the action of dilute acid on the cellular substance furnish a serum which gives the Widal test.

9. Vaccination of guinea-pigs against typhoid fever is practicable. A single vaccination will protect the animal against subsequent intra-abdominal injection of many times the minimum lethal dose.

Dr. Leach has continued her studies of the chemistry of the colon bacillus, and I hope that her work will soon give us some very definite and positive information concerning the chemistry of the bacterial cell. I must content myself at present with the statement that she has obtained in crystalline form xanthin bases, hexon bodies, and monoamido acids. I cannot at present say whether these bodies are identical with similar substances obtained from proteids or not. This is an interesting question and one upon which much close and careful work must be done before its solution can be recognized as altogether satisfactory.

Walter Vaughan has continued his studies of the anthrax toxin, and by using a culture of but slight virulence he has secured an intracellular toxin which kills animals, both those susceptible and those insusceptible to anthrax infection, in quantities of about 1 part of the poison to 2500 parts of body weight. It is hoped that a vaccine consisting of dead germ substance may be obtained for this disease.

TREATMENT OF MIGRAINE.

By B K. RACHFORD,
OF CINCINNATI, OHIO.

Migraine is an autointoxication which commonly finds expression in recurrent, self-limited attacks of paroxysmal headache, usually accompanied by nausea, vomiting, vertigo, visual phenomena, and other vasomotor and sensory disturbances.

In the treatment of migraine I assume the following hypotheses :

1. While autointoxication is the essential factor in every case it should also be noted that a neurotic inheritance, overtaxation of the nervous system, and reflex irritation may be contributing etiologic factors in any individual case.

2. The poisons which produce migraine are under normal conditions largely destroyed or converted into harmless products by the liver. These poisons are, therefore, increased by all conditions that diminish the functional capacity of the liver, such as indoor life and lack of exercise, and by all conditions that throw increased work upon the liver, as excessive eating and alcohol drinking.

3. Under pathologic conditions, either through a weakened functional capacity of the liver or through excess of poisons produced, the liver is no longer able to destroy these poisons, and a periodic acute functional incompetency of this organ results, thereby throwing these poisons into the general circulation and producing an acute autointoxication (migraine).

4. Under aggravated pathologic conditions the liver may remain for a long time in a state of chronic incompetency, thus allowing the greater portion of these poisons to filter through into the general circulation, producing a state of chronic autointoxication (chronic migraine with neurasthenic symptoms). In this condition the liver is commonly enlarged.

5. A faulty metabolism of albuminoids, occurring both in the body tissues and in the intestinal canal, plays a rôle in the etiology of migraine.

6. Migraine is commonly associated with constipation and resulting abnormal intestinal fermentation.

7. The poisons which produce migraine commonly act through both the sensory and sympathetic nerves of a part, producing both pain and vasomotor disturbances. The younger the patient the more marked are the vasomotor disturbances, and the less marked are the sensory, and *vice versa*. This is a rule which may have exceptions. Very commonly the poisons may at the same time attack the sensory nerves of one part, producing pain (headache), and the sympathetic nerves of another part, producing vasomotor disturbances (vomiting).

8. The symptoms of a migrainous attack will vary with the part attacked, the nerves involved, the virulence and character of the poisons, and the age and physical condition of the patient.

9. The ordinary type of migraine, which is manifested by recurrent self-limited attacks of unilateral headache associated with nausea, vomiting, vertigo, and visual disturbances, may have many variations as to symptoms and yet be migrainous, in the sense that the attacks have the same etiology and yield to the same treatment.

Among such variations may be classed periodic depression of spirits, periodic tachycardia, recurring attacks of dyspepsia without apparent cause, recurrent attacks of severe gastric pain and vomiting not associated with headache, and in younger patients recurrent vomiting and recurrent coryza not associated with pain in the stomach or head.

About puberty, in rare instances, the migrainous attacks may become epileptoid in character.

Treatment. The purpose of this paper is to outline a treatment of migraine which I have employed with good success during the last ten years.

Medical Treatment for Relief of Constitutional Condition. Since migraine is a chronic disease and the treatment must be continued over many months, it is absolutely necessary, for permanent success in the treatment of this condition, that the medical treatment should be as simple and as palatable as possible. This is true of men,

women, and children alike. The busy man cannot, as a rule, be prevailed upon to take over a long period of time three or four doses of medicine each day, and women and children, as a rule, after a few weeks of treatment, prefer the disease to taking dose after dose of unpalatable medicine throughout an entire season. The keynote of success, therefore, in the treatment of migraine is in the simplicity and palatability of effective medication. To accomplish these desiderata some ten years ago I devised a formula which is here presented with such slight changes as time and experience have suggested :

℞.—Sodii sulphatis (dry)	30 grains.
Sodii salicylatis (from wintergreen)	10 "
Magnesii sulphatis	50 "
Lithii benzoatis	5 "
Tincturæ nucis vomicæ	3 drops.
Aquæ destil. to make	4 ounces.—M.

This prescription is made in a large quantity by a reliable pharmacist and then sent by him to a mineral-water factory to be put up in siphons and charged with carbonic acid. These siphons are sold on prescription at fifty or sixty cents each, with a good margin of profit to the pharmacist.

These siphons I prescribe under the name of " Siphon C," and direct my adult patients to take from one-quarter to one-half glass of this carbonated medicine each morning on arising, half an hour or more before breakfast. It is important that the dose should be so regulated as to produce a slightly laxative but not cathartic action. Only one dose of this medicine is given in twenty-four hours, and after the patient is fairly under treatment this is commonly the only medicine used.

I know from a very long experience that the above prescription may be given for an indefinite length of time (years if necessary) without losing its great therapeutic value or producing disgust for it on the part of the patient. I have yet to find an adult patient who would not continue the taking of this medicine as long as I desired. After the first week or ten days patients grow accustomed to it, and then even the most sensitive women no longer object to its use. This medicine, moreover, is not contraindicated by any condition of the stomach. It is, in fact, one of the most valuable formulas I have found for the treatment of chronic gastric catarrh

and chronic ulcer of the stomach. The condition of the stomach need not deter us, therefore, from prescribing this formula. On the other hand, "a bad stomach" is a further indication for its use.

I do not hesitate to say that the action of the above siphon medicine, when combined with proper dietetic and hygienic treatment in the relief of migrainous symptoms, furnishes one of the most satisfactory examples of the action of drugs in the relief of symptoms, that can be found in the whole range of the materia medica.

I wish especially to insist that the use of the above formula will give better results than the separate use of the various medicines which it contains. The great value of the formula, however, depends upon the fact that it combines palatability and simplicity with efficacy of medication; and these advantages enable one to treat an essentially chronic condition by giving a single dose of medicine in a day.

It is my habit in the treatment of this condition to continue the above siphon medicine through the winter months only, discontinuing its use about April or May.

Patients under this treatment often go through the winter months without a single attack of migraine. On discontinuing the medicine, however, in April or May, when the climatic conditions make it no longer necessary, I usually advise my patients to report to me again about the first of the following January, or earlier, of course, if there is any return of the migrainous symptoms. At this time they are again placed upon the siphon medicine, and advised to continue it until the following spring. By this plan of giving the above formula for three or four months in the year I have succeeded in controlling migrainous symptoms in a large number of patients.

In studying the ingredients of this formula one finds the medicines that have been used for many years in the treatment of this condition. Magnesium sulphate is necessary to overcome the constipation which is present in nearly all of the cases, and by its action we unload the portal circulation and eliminate the poisons through the intestinal canal.

Sodium sulphate acts very much in the same manner, plus the cholagogue action. Lithium benzoate probably also acts as an intestinal antiseptic, and probably as an eliminator through the

kidneys. The small amount of nux vomica which the formula contains is added largely to cover the soapy taste of the formula, and thereby make it more palatable. Sodium salicylate (wintergreen) is the remedy par excellence of the prescription. This remedy not only acts as an intestinal antiseptic, but increases the functional activity of the liver.

There are two other siphon formulæ which I occasionally use in the treatment of migraine. They are as follows :

SIPHON B.

℞.—Sodii sulphatis (granulated) . . . . . 2 drachms.
Sodii phosphatis (granulated) . . . . . 1 drachm.
Sodii salicylatis . . . . . 10 grains.
Tincturæ nucis vomicæ . . . . . 3 minims.
Aquæ destil. to make . . . . . 4 ounces.—M.

S.—Take each morning.

SIPHON A.

℞.—Potass. bicarbonatis . . . . . 20 grains.
Rochelle salt . . . . . 1 drachm.
Sodii salicylatis . . . . . 5 grains.
Tincturæ gentian. comp. . . . . ½ ounce.
Aquæ destil. to make . . . . . 4 ounces.—M.

S.—Take each morning.

Siphons B and A may be used in those cases in which Siphon C is too laxative in its action. Siphon A is especially valuable in those cases of migraine suffering from irritable bladder or muscular rheumatism.

In the beginning of the treatment, however, in addition to the siphon medication, I always prescribe one of three drugs—sodium benzoate, sodium salicylate, or cannabis indicæ—and I further advise the drinking of water between meals.

Sodium benzoate may be prescribed in twenty-grain doses taken after lunch and dinner. This dose may be more palatable by taking it in peppermint-water or in some carbonated water.

Sodium salicylate (wintergreen) may be given in capsules in three to five-grain doses after lunch and after dinner.

The proprietary preparation known as colchisal may be given in the same manner, one capsule after meals. I have found it to be a most valuable aid in the treatment of long-standing cases associated with other gouty symptoms.

Salol may be the form of the salicylate chosen for the treatment of this condition in children. I have also used salicin very largely

in the treatment of these cases, but, I think, with not such good results as I have obtained from the above-named remedies.

Cannabis indica, in one-quarter-grain doses two or three times a day, is of very great value in controlling the paroxysms of migraine, and may be used for three or four weeks, until the patient is well under the siphon treatment. I not infrequently combine the cannabis indica in a capsule with sodium salicylate or salol in the treatment of these cases.

With these drugs to aid the action of the siphon medicine, the paroxysms of migraine may be controlled almost from the beginning of the treatment. After the patient, however, has been under treatment for from three to six weeks all medication other than the siphon medicine may be discontinued.

In some of the cases, however, it is necessary to give an intestinal antiseptic throughout the treatment of the case, and for this purpose I commonly use a one-grain salol-coated pill of potassium permanganate, taken after meals. This pill, which I devised many years ago and have used continuously ever since, has proven very efficacious in my hands. Dr. M. Allen Starr has modified this pill under the following formula:

℞.—Sodium sulphocarbolate . . . . . 5 grains.
Kal. permangan. . . . . 1 grain.
Betanaphthol . . . . . 1 grain.—M.
S.—One after meals and at night.

This pill is coated with shellac and is of value in those cases requiring an intestinal antiseptic.

In 1895[1] I published a paper upon this same subject in which I recommended the use of the following formula:

℞.—Sodii salicylatis (wintergreen) . . . . . 2 drachms.
Sodii phosphatis (dry) . . . . . 4 drachms.
Sodii sulphatis (dry) . . . . . 10 drachms.—M.
S.—A teaspoonful, more or less, to be taken in a glass of Seltzer water each morning.

These salts I still prescribe for patients travelling or otherwise so situated as to make it impossible for them to get the siphon medicine.

There is one other drug that has long held a deservingly high reputation in the treatment of migraine, and that is mercury, either in the form of calomel, blue mass, or the gray powder. Either

[1] Medical News, September 7, 1895.

calomel or blue mass is a good drug to begin the treatment of a case of migraine, and even after the patient has been placed upon the siphon medicine it may occasionally be beneficial to supplement this treatment with a few doses of calomel or a dose of blue mass.

The gray powder of mercury I have used with great advantage in the treatment of migrainous conditions in children[1] too young to take the siphon treatment. In such patients a laxative formula, such as the following, may be substituted for the siphon medicine:

℞.—Sodii sulphatis . . . . . 2½ drachms.
Magnesium sulphatis . . . . . 5 "
Lithii benzoatis . . . . . 2 "
Aquæ destil. to make . . . . . 3 ounces.
Elixir tarax. . . . . 3 ounces.—M.

S.—Tablespoonful before breakfast for a child of eight years.

In the treatment of migrainous cases I have occasionally noticed that after a prolonged use of the siphon treatment patients become slightly nauseated, the tongue becomes furred, and there is a dull headache with loss of appetite. In this condition dilute nitro-muriatic acid acts almost as a specific, but during the time that the acid is given, compound licorice powder or cascara sagrada may be substituted for the siphon medicine. After a week of such treatment the siphon medicine may be resumed.

Treatment of Attack. The migrainous attack is best treated by rest in bed in a dark room without food. This with hot fomentations to the forehead and a dose of calomel or blue mass will suffice to relieve milder attacks. When the attacks are more severe, however, the following prescription, if taken early in the attack, will usually give relief:

℞.—Caffein citrate . . . . . 2 grains.
Antipyrin . . . . . 10 grains.
Potassium bromid . . . . . 30 grains.—M.

S.—To be taken in half a glass of water.

If for any reason it is not desirable to give antipyrin in these attacks, ten grains of sodium salicylate may be substituted for the antipyrin in the above prescription. Either of these prescriptions will be found very efficacious in relieving the severe pain of migrainous attacks. Occasionally, however, the attack may be so severe as to demand the use of morphin hypodermically. Fol-

[1] In 1897 I published in the Archives of Pediatrics a series of papers on the treatment of this condition in infants and children.

lowing the attack the routine treatment as above outlined may be resumed, and when the patient is well under this treatment the paroxysmal attacks, as a rule, cease.

Preliminary Treatment. In the beginning of the treatment of a case of migraine it is important to search for reflex factors that may possibly play a rôle in producing the paroxysms. Such reflex factors are often found in ocular defects producing eye-strain, in abnormal conditions of the nose and pharynx, such as adenoids and hypertrophies, and in diseases of the pelvic organs.

It is not an uncommon experience to have migrainous attacks almost disappear on the removal of some aggravated pathologic condition which is causing reflex irritation of the nerve centers. This does not, however, prove that the reflex is the sole factor in producing the migraine in these cases. It does, however, prove that these factors are so important that it would be folly to attempt the constitutional treatment of such cases without the removal of reflex factors. I do not believe, however, that simple reflex headaches which are entirely cured by the removal of a reflex cause are to be classed under the heading of migraine.

Migraine is, as I believe, a constitutional disease, due to an autointoxication, and with this condition there may coexist a cause of reflex irritation to the nervous system so important that it is impossible to completely cure these cases without the removal of the reflex factor.

Dietetic and Hygienic Treatment. All that has been said in the way of medicinal treatment will be of little avail unless it goes hand in hand with proper dietetic and hygienic treatment. The most important bit of dietetic advice that can be given to a migrainous patient is that he should not eat too much. Most of these patients are in the habit of eating more than is necessary. It is important, therefore, that any tendency in this direction should be restrained. There are also certain articles of diet which should be partaken of sparingly or not at all—coffee, alcohol, red meats, and sweets should, for a time at least, be almost if not quite eliminated from the diet.

Patients may be allowed milk, eggs, fish, oysters, the white meat of poultry, cereals, fruits, and well-prepared vegetables, provided a feeble digestion or some idiosyncrasy on the part of the

individual does not exclude one or more of the above articles from his diet list. The diet to be prescribed in any individual case will, of course, depend upon the age of the patient as well as upon his digestive capacity and the character of life he leads.

Exercise in the open air is scarcely less important than diet in the treatment of migrainous cases. All kinds of outdoor athletic sports are to be advised, and among these horseback riding is one of the best. The financial condition, the age, and the inclinations of the individual patient will suggest to the physician the character of outdoor exercise to be recommended. General massage is of great value in the early treatment of patients of feeble constitution.

Before closing the subject of the treatment of migraine, I would call attention to the great value of certain hydrotherapeutic measures in the treatment of selected cases. The Turkish and vapor baths as well as hot alkaline tub baths are of benefit, especially in patients of rather stout and robust constitutions. These baths are more efficacious when accompanied by large potations of water and followed by general massage.

A CASE OF CHRONIC LYMPHATIC LEUKEMIA WITHOUT ENLARGEMENT OF THE LYMPH NODES.

By GEORGE BLUMER, M.D.,
OF TROY,

AND

HERMON C. GORDINIER, M.D.,
OF ALBANY, N. Y.

Our knowledge of the pathology of leukemia is intimately dependent on our knowledge of the development of the different forms of white blood cells and their relation to the blood-forming organs. In conditions such as leukemia, where there is disagreement as to the origin of the disease, a case which varies from the disease type may often throw more light on the problem than one which is typical. We therefore venture to report the following case, which differs from the ordinary case of lymphatic leukemia in many respects.

The following is a summary of the main facts from a clinical and pathologic standpoint:

Mrs. J. G., aged forty-five years, a housewife.

Family History. Her father and mother are dead, of unknown causes. One of her sisters died of cancer of the liver, secondary to gallstones. She has two sisters and one brother living and well.

Personal History. The patient was married at twenty-one. She has had five children. Three are living and well. One died of scarlet fever and the other of some obscure disease. She has never been ill since childhood, save with childbearing, until the onset of the present illness.

Present History. The patient consulted Dr. Gordinier at his office two weeks prior to her death, with the statement that her present illness began about one year ago, with breathlessness and fatigue on exertion, together with diminution of appetite and dizziness. These symptoms have gradually increased, and have been accompanied by a gradually increasing pallor of the skin. At present there is marked dyspnea on the slightest exertion. She cannot lie recumbent, but in order to be comfortable must be propped up in bed with pillows. She has had at no time diarrhea or stomach dis-

turbances of any kind. She says that she has never been jaundiced or bled from the nose, gums, mouth, or rectum, and her menstruation was always normal in amount and without discomfort up to two years ago, when it ceased.

Present Condition. She is moderately well built; weight, 150 pounds. She is of a dingy, yellow complexion. The conjunctiva are pearly white and all visible mucous membranes are exceedingly pale. There is no apparent general emaciation. The musculature is everywhere flabby, and there is soft edema of the legs, especially about the ankles and along each tibia. The pulse is rapid, easily compressed, regular, and evidently of very low tension. The arterial walls are not thickened. The respirations are somewhat hurried—24 per minute. There are no dilated veins over the chest or abdomen. The apex beat is feeble, diffuse, and appears displaced slightly downward and outward. The area of cardiac dulness begins above, at the fourth rib, and extends from the midsternal line 2½ cm. to the left of its normal position in the fifth intercostal space. There is no bulging of the precordia, thrill, or friction fremitus. At the apex a soft, blowing murmur is heard, which is conducted rather faintly to the midaxillary line. Over the aortic interspace there exist a soft systolic and a diastolic murmur, the latter being very soft and conducted a short distance over the body of the sternum, but not heard at the apex. A distinct venous hum is heard on each side of the neck. The carotids pulsate rather prominently, but no murmur is heard over either of them. There is no double tone heard in the femorals. There is no capillary pulse. The lungs are negative, save for the physical signs of a moderate degree of emphysema. The superficial fat is well developed. The splenic dulness begins at the eighth rib, in the midaxillary line, and extends downward to the eleventh rib. The spleen may be palpated by thrusting the hand slightly beneath the left costal border. The liver dulness begins beneath the fifth rib and extends about 2 cm. below the free border of the ribs. It is easily palpated. Its lower border presents nothing abnormal. On the outer surface of the right thigh, just above the knee, exists a well-defined, rather oblong, somewhat irregular scar, due to an old injury. No evidence of any syphilitic lesion could be found. The stomach tympanicity was carefully mapped out after inflation and found to occupy its normal area. The abdomen was universally tympanitic, soft, and presented no flatness in either flank. The rectum and the uterus presented nothing abnormal. There was tenderness on percussion over the lower part of the sternum and over the lower costal cartilages, as well as of the long bones of the lower extremities. There was no tenderness on percussion of the skull or over the splenic or hepatic regions.

Glandular System. The most careful search failed to disclose the slightest enlargement of the lymphatic apparatus, either superficial or deep. The mouth, throat, and larynx showed a very pale mucous membrane, but no enlargement of the tonsils or follicles. The tongue was pale and coated with a slight, yellowish fur. It was protruded straight, and was movable in all directions. The gums were exceedingly pale and not vascular.

Nervous System. The cranial nerves were all normal. The optic disks showed none of the characteristic changes often found in leukemia. The pupils were midwide and presented normal reactions. Hearing was acute in each ear. The patient's gait presented nothing abnormal, save that it was an effort for her to walk, owing to her great weakness and the fatigue excited thereby. The motor power seemed fairly good. There was no sensory disturbance, no patches of anesthesia, no ataxia. Both the superficial and deep reflexes were normal. She had perfect control over the organic reflexes. The muscles, though flabby, were not apparently atrophic, and were not tender on pressure. There was no tenderness of the accessible peripheral nerves. The skin was pale, not thickened, and presented no eruptions.

The urine was amber color; specific gravity, 1022. It contained no albumin, sugar, casts, or blood, but a rich deposit of uric acid.

The day before her death all the above-mentioned subjective symptoms were greatly exaggerated, and the pallor seemed much increased. There was marked dyspnea, the patient lying semirecumbent in bed, evidently suffering from intense air-hunger. There was no cyanosis. The heart was rapid. The muscular element of the first sound was very weak. The pulse was 140 and the temperature 104° F. There were numerous subcrepitant râles at the bases of the lungs posteriorly, doubtless due to beginning pulmonary edema The tenderness over the bones was increased. Liver and splenic dulness was not changed.

The Blood. At the time of the first visit a blood examination showed the following: hemoglobin (Dare, Gowers), 35 per cent.; red corpuscles, 1,625,000; leukocytes, 130,000. The blood to the naked eye appeared watery and had a whitish tinge.

A differential count of 1000 leukocytes showed the following: polynuclears, 3.3 per cent.; large mononuclears, 1 5 per cent.; transitionals, 0.9 per cent.; small and medium-sized mononuclears, 94 per cent.; eosinophiles, 0.1 per cent.; mast-cells, 0.1 per cent.; myelocytes (neutrophilic), 0.1 per cent.; nucleated reds (normoblasts), 18 per cent. The day before the patient's death the hemoglobin had fallen to 30 per cent.

Microscopic Examination of Stained Specimens. The *red corpuscles* present a moderate amount of variation in size. There are a very few, if any, macrocytes, but a good many microcytes are seen. A slight degree of poikilocytosis is present. The red cells show a central pallor. Nucleated reds are occasionally seen, all of the normoblast type.

The *leukocytes,* as shown by the differential count, diverge greatly from the normal. The prevailing type of cell is a mononuclear element, resembling the small mononuclear cell of normal blood, from which, however, it differs in certain respects. This cell is about the size of the red corpuscles, though sometimes smaller and sometimes larger. It possesses a spherical nucleus surrounded by a very narrow zone of protoplasm. The nucleus is usually fairly regular, but at times shows slight flattening or indentation on one side. It stains with moderate intensity and shows a well-marked nuclear network, with occasional nodular swellings, but no definite nucleoli. The

protoplasm, which is often more apparent on one side of the nucleus than on the other, is free from granules, and stains, as a rule, faintly pink with Ehrlich's triple stain. Occasionally the protoplasm is basophilic rather than acidophilic, but this is the exception. Some of these cells suggest very strongly nucleated reds, but comparison with nucleated reds in the same blood shows that they possess a much larger amount of protoplasm, staining much pinker, and a more solid, more deeply staining nucleus.

A second type of leukocyte, present in very much smaller numbers than the form just described, was about midway in size between the small mononuclear and the normal large mononuclear of the blood. These cells possess a much larger amount of protoplasm than the first variety, the amount of protoplasm varying in different cells. The nucleus, which is quite often extracentral, is spherical or ovoid, as a rule, though at times flattened on one side or indented. The nucleus stains less intensely than that of the smaller cells. The chromatin network is rather coarse and shows in many instances nodular thickenings about the edge of the nucleus, resembling those seen in the ordinary plasma cell. The protoplasm is free from granules and is acidophile.

The third type of cell occasionally seen was a very large, oblong, faintly-staining body devoid of granules or of nucleus, and evidently in an advanced stage of degeneration. These cells resemble the large, degenerated forms described by various observers in cases of acute lymphatic leukemia.

Typical polynuclears, large mononuclears, and transitionals are occasionally noted. One eosinophile, one neutrophilic myelocyte, and one mast-cell were observed in counting one thousand leukocytes. The blood plates appear normal in amount.

The patient died ten days after she was first seen, and the autopsy was performed ten hours after death, the weather being cool.

The anatomic diagnosis was as follows:

Lymphatic leukemia with very marked changes in the bone-marrow and with practically no changes in the lymph glands. Edema and congestion of the lungs. Marked fatty degeneration of the heart muscle. Swelling of the spleen. Marked cloudy swelling of the kidneys, with "multiple superficial areas of necrosis" (?). Small stone in the pelvis of the left kidney. Slight chronic, passive congestion of the liver, with cholelithiasis.

The following are the notes made at the autopsy:

Body 165 cm. in length; strongly built; well nourished; marked rigor mortis; slight lividity of the dependent parts; surface is pale; the left leg is larger than the right, and edematous; mucous membranes are extremely pale; the superficial glands are not palpable; the subcutaneous fat is moderate in amount and unusually yellow; the muscles are well developed.

The peritoneal cavity is perfectly dry; both layers are smooth. The omentum is free from adhesions and contains a moderate amount of fat. The glands are not apparent. The appendix is retroperitoneal; runs upward immediately in front of the right kidney and is transformed into a fibrous cord, in which no lumen is apparent. The foramen of Winslow is open.

Diaphragm: Right side, fourth rib; left side, fourth space.

The axillary glands of the left side are very slightly enlarged, the largest found being 15 mm. in diameter and slightly whiter and more opaque-looking than normal. The mammary glands are normal-looking.

The costal cartilages are not ossified.

The precordia measures 10 x 10 cm.

The pericardium contains 60 or 70 c.c. of clear fluid. Two or three white nodules of connective tissue are present on the parietal pericardium. The visceral pericardium is normal.

Heart: The right side of the heart contains fluid blood and postmortem clots of a pinkish color covered with an irregular, gray coating. The endocardium and valves of the right side are normal. The average thickness of the right ventricle is 5 mm. The left side of the heart is almost empty, except for a clot adherent to the mitral valve. The valves on the left side are normal; endocardium also normal. The heart muscle is flabby and shows a well-marked faded-leaf appearance, especially in the papillary muscles. The coronary arteries show a few patches of early atheroma. The auricular appendages are free from clot. The foramen ovale is closed.

The left lung is adherent by old adhesions posteriorly and laterally over the lower lobe. The lung is everywhere crepitant, but feels much firmer than normal. On section, both lobes are slightly congested and markedly edematous. The bronchi contain frothy mucus. They appear normal. The large bloodvessels contain postmortem clots.

The right lung is free from adhesions. It is crepitant throughout and presents in every way the same appearance as the left. The bronchi and vessels are as on the other side. The bronchial glands are not enlarged, but are deeply pigmented. They show no signs of tubercles.

The spleen is free from adhesions. It is much enlarged and measures $16 \times 10\frac{1}{2} \times 5\frac{1}{2}$ cm. The surface is smooth. The consistency is much softer than normal. On section the pulp is increased. The Malpighian bodies are only occasionally to be made out and are not enlarged. The trabeculæ of the spleen do not appear to be increased in amount.

The liver is free from adhesions. It is considerably enlarged and measures $24 \times 20 \times 9$ cm. The capsule is smooth. The consistency is softer than normal. On section the centers of the lobules are slightly congested; their peripheries are pale. Scattered through the organ are a very few slightly opaque, rounded nodules not larger than miliary tubercles, which suggest lymphomata.

The gall-bladder contains sixty-three faceted gallstones, varying in diameter from 0.5 to 1.5 cm., of a very low specific gravity, and apparently consisting of a nucleus of bile salts surrounded by cholesterin.

The left adrenal is normal in appearance, except for a postmortem cavity.

The left kidney measures $11\frac{1}{2} \times 5\frac{1}{2} \times 4\frac{1}{2}$ cm. In the apex of one of the calices is an almost black, firm calculus 3 mm. in diameter. The capsule strips easily, leaving a pale surface. Dotted over the surface are exceedingly numerous, rounded, opaque, white areas just on the border of visibility.

They do not impress one as lymphomata, but rather as some form of degeneration. On section, an occasional similar area is seen. The pallor of the kidney is still apparent. The cortex averages 7 mm. in width. The cortex markings are almost absent. Most of the glomeruli are pale; a few are congested. The pelvis is normal.

The right adrenal shows postmortem change.

The right kidney measures $11\frac{1}{2} \times 5 \times 4\frac{1}{2}$ cm. Its appearance is the same as its fellow.

The ureters are normal.

The bladder is normal.

Uterus: The external os contains one or two fresh-looking clots. The vagina is normal. The glands of Naboth are enlarged, forming cysts. The uterine wall is thickened, averaging 2 cm. in thickness. The endometrium is pale and slightly thickened. The tubes are free from adhesions and normal-looking. The ovaries are partly sclerotic, especially the right. The left contains a fairly fresh corpus luteum.

Rectum: The mucous membrane is pale and the follicles are distinctly enlarged.

The mesenteric lymph glands are but slightly, if at all, enlarged. Some of them are congested; others pale. The retroperitoneal lymph glands are not enlarged. Glands which can be definitely made out to the naked eye as hemolymph glands are not apparent. The glands in the hilum of the liver, the perigastric glands, the peripancreatic glands, the posterior mediastinal, the iliac glands, and the inguinal glands are not enlarged, although the inguinal glands on the left side appear a little firmer than normal and are slightly opaque.

The aorta shows a few patches of fibrous and fatty atheroma.

The stomach is dilated. The mucous membrane is pale and covered with sticky mucus. The pancreas is perfectly normal. The bone-marrow of the left femur has lost entirely its yellow appearance, and is converted into lymphoid marrow. The bone-marrow of the right femur is the same as that of the opposite side, of a mottled, grayish-red color.

Intestines: One or two of Peyer's patches show a shaven-beard appearance. The solitary follicles are slightly swollen just above the valve and in the large intestine.

Microscopic Examination. Bone-marrow: The bone-marrow of the femur is completely transformed into a tissue resembling lymphatic tissue. Under the low power it appears as closely packed mononuclear cells separated by a fine reticulum, and containing occasional blood channels, some of which are markedly dilated. With higher powers the predominating cells are mononuclear elements resembling those seen in the circulating blood. The larger number of these are about the size of a red blood cell; if anything, rather larger than a red corpuscle. These cells have a rounded nucleus, staining rather darkly with hematoxylin, and with a fairly well marked, rather coarse, chromatin network. The chromatin network shows occasional thickening, but no definite nucleoli. The protoplasm varies in amount, but is

usually scant, and stains faintly with eosin. Next in number to these cells are much larger mononuclear elements with a rounded nucleus, often situated extracentrally, and a good deal of protoplasm. The nucleus stains a trifle more faintly than that of the smaller cells, but has the same marked chromatin network, which tends to be concentrated at the periphery of the nucleus. Definite nucleoli are present in many of these cells. The protoplasm is markedly acidophile. No granules are present in the protoplasm of either of these types of cells, which form the great mass of the elements found in the bone-marrow. Besides these cells there are seen a few myelocytes, both eosinophilic and neutrophilic, and a very few bone-marrow giant cells, distorted in shape, with degenerated nuclei and protoplasm. A very few polynuclears are seen. Red cells are present in rather small numbers, but nucleated reds are scarce and of the normoblast type. The dilated blood spaces contain an excess of the two types of mononuclear cells described. Quite a large number of the mononuclear cells showed evidences of direct division. Indirect division was not noted, though pictures suggesting this were occasionally seen. The red bone-marrow showed a similar lymphoid condition.

The lymph glands: The picture varies in different glands. In the hemolymph glands the gland appears as if injected with leukemic blood, the sinuses being distended with red blood corpuscles and leukocytes of the types found in the circulating blood. No evidence of proliferative changes in the gland structures are apparent, though the endothelial elements have proliferated in places. The ordinary lymph nodes do not all present the same appearance. In some, and especially the retroperitoneal lymph nodes, a chronic lymphadenitis of a patchy character is present, quite large areas of gland tissue being replaced by a dense connective tissue. Many of the lymph nodes, particularly the smaller ones, are with difficulty to be distinguished from the bone-marrow at first glance. The germinal centers have entirely disappeared, and the sinuses are so closely packed with mononuclear cells that the absence of red cells is the only feature which rules out the bone-marrow. Under the higher powers the resemblance to the lymphoid bone-marrow is still quite striking, for the cells composing the lymph glands are mononuclear elements of the two types predominating in the bone-marrow, and in places giant cells of the bone-marrow type occur in small numbers. The proper cells of the lymph gland can be distinguished from the mononuclear cells of bone-marrow origin by their tinctorial characters, and show no evidence of proliferation. The endothelial cells along the trabeculæ are, in places, proliferated, and have taken on phagocytic properties.

The intestine: The lymphatic apparatus of the intestine is diffuse. The follicles are not sharply defined, but shade off into the submucosa. Changes similar to those seen in the lymph nodes are present in the lymphatic apparatus, and the submucosa is infiltrated to a slight degree with mononuclear cells similar to those seen in the blood.

The spleen: There is a diffuse infiltration of the pulp with mononuclear

cells, so that the Malpighian corpuscles are, as a rule, not seen as localized collections of cells, but blend into the surrounding pulp. The cells are of the types which predominate in the bone-marrow and lymph glands. An occasional eosinophile myelocyte is seen, and in one section a cell resembling a bone-marrow giant cell was met with. Nucleated red blood cells are also present, but in no larger proportion than they occur in the peripheral circulation. There is no evidence of increased blood destruction or of proliferation of the lymphatic apparatus. The finer trabeculæ are slightly increased in some areas, but there is no increase in the larger trabeculæ.

The liver: The liver cells are swollen and granular, and occasional fatty cells are seen. The cells do not contain hemosiderin. The capillaries are narrowed by the swollen cells, and the blood in them shows the same excess of mononuclears seen elsewhere. Nucleated red corpuscles are no more numerous than in the circulating blood. Definite lymphomata are not present, though the portal connective tissue is more or less extensively infiltrated with mononuclear cells of the types seen in the blood.

The kidney: Aside from marked cloudy swelling and the usual blood changes the kidney shows nothing of importance.

The heart-muscle shows a slight increase in the interstitial tissue about the larger vessels. The muscle cells are, many of them, vacuolated.

The voluntary muscles show a moderate number of encapsulated trichinæ. The remaining organs show nothing of importance.

At the present time writers on the pathology of leukemia may be divided into two groups. One group, in which Ehrlich is the central figure, holds that myelogenous leukemia results from disease in the bone-marrow, and lymphatic leukemia from disease in the lymph glands. The other group, influenced by the views of Neumann, believes that leukemia, no matter what the blood picture may be, is always primarily a disease of the bone-marrow. Pappenheim is, perhaps, the most prominent exponent of this group.

The view of Ehrlich, which his coworkers Lazarus and Pinkus share with him, is markedly influenced by his ideas as to the origin of the different forms of leukocytes. He denies the presence in the bone-marrow, under normal circumstances, of cells corresponding to the lymphocyte of the blood, and claims that the only non-granular mononuclear cell constantly found in the bone-marrow is a cell which corresponds to the large mononuclear leukocyte. He believes that the lymphocyte originates in the lymph glands and other lymphatic tissues. It is obvious that, holding these beliefs, he cannot logically admit lymphatic leukemia as primarily a disease of the bone-marrow.

As Reed has pointed out, the conclusions of Ehrlich's school are open to the criticism that they are based largely on studies of the morphology of the blood and the clinical study of cases, while the study of the bone-marrow has been relatively neglected.

On the other hand, the exponents of the bone-marrow origin of leukemia, Pappenheim, Walz, Reed, Bradenburg, and others, have relied on their studies of the hematopoietic organs for their conception of the pathology of the disease. They, as well as other observers, have constantly found in normal bone-marrow cells which are indistinguishable from the lymphocytes of the blood, and they can, therefore, logically conceive of a lymphatic leukemia originating from changes in the bone-marrow alone.

The case here reported resembles in all important respects similar cases reported in the last few years, particularly cases reported by Pappenheim and Reed. The clinical picture of all these cases suggests a severe anemia; in one of Pappenheim's cases and in our case it was suggestive of pernicious anemia. The course of most of the cases is acute, though in our case and one of Pappenheim's the history indicated an illness of at least a year's duration. The striking features in the pathologic examination are the marked lymphoid change in the marrow of the long bones and the absence of enlargement of the lymph nodes and lymphatic apparatus generally. The histologic changes strongly indicate that the bone-marrow lesion is the primary one, and that the excessive escape of leukocytes into the blood takes place from the diseased marrow. The changes in the lymphatic apparatus indicate that the part played by it is a passive rather than an active one.

The points of interest in these cases lie in the blood changes, the bone-marrow changes, and the relation of such cases to leukemia in general and to allied diseases.

The main interest in the blood changes relates to the character of the mononuclear cells which show such marked increase. While they resemble quite closely the normal lymphocyte, they present points of difference, the most important of these being the acidophile character of their protoplasm. Both Pappenheim and Rubenstein believe that lymphocytes and red blood corpuscles may originate from an ancestral cell which is common to both, a view which Reed supports. The latter observer suggests that the cells which predominated in her case,

which are undoubtedly the same cells that predominate in our case, possibly represent such an ancestral cell. It is necessary to state, however, that the tinctorial behavior of the protoplasm in the mononuclear elements in our case and in Reed's does not correspond in most instances to Pappenheim's description of his ancestral cell (myelogonie), nor to Rubenstein's "mother cells," both of which are said to have faintly basophilic protoplasm. While some of the elements increased in our case have a basophilic protoplasm, others have faintly but distinctly acidophilic protoplasm. It is questionable, however, whether the possible identity of these different cell forms should be excluded merely on account of slight tinctorial differences in the protoplasm. If we accept the view that these cells represent ancestral cells, it would seem necessary to assume that for some reason these cells, which show evidences of marked activity as far as reproduction is concerned, have lost their power of developing beyond a certain point, *i. e.*, they are no longer capable of completing their cycle of existence. This is shown by the fact that both nucleated red cells and typical lymphocytes are extremely rare, both in the bone-marrow and in the circulation. It is difficult to imagine why cells which show such marked evidences of proliferative activity should lose their function of differentiation, unless it is that their rapid extrusion into the blood current places them in a medium unfavorable for their further development. If such a theory of arrested development of an ancestral or, as Reed calls it, a mother cell is tenable, it would explain both the anemia and the lack of typical lymphocytes.

On the other hand, it cannot be denied that these cells may be merely an early stage of the ordinary lymphocyte such as is not found in the peripheral circulation under normal circumstances. The assumption that they represent an ancestral cell is strongly suggested by their close resemblance to lymphocytes, their acidophylic protoplasm, and their resemblance to nucleated red cells, but, as Reed very properly says, the staining reaction of the cell protoplasm is a slight and variable criterion on which to base cell relationships, and we may add that this is especially so when we are dealing with the ordinary acid dyes for which the protoplasm of so many varieties of cell possess an affinity.

The larger mononuclear elements described in this case cannot be sharply separated from the group just discussed, inasmuch as their

size and certain slight differences in their nuclei seem insufficient grounds for placing them in a separate class; furthermore, cells are seen in the blood which seem to connect these two groups.

The change in the bone-marrow in this case, as in similar cases reported, would seem to be best classed as a hyperplasia. This would also seem to be the lesion in splenomyelogenous leukemia and in leukocytosis, the essential difference in the changes in these diseases being a qualitative one. Why in one instance the hyperplasia should affect all the elements of the bone-marrow, as is the case in myelocytic leukemia, and in another only the mononuclear elements should be involved, as in lymphoid leukemia, it is difficult to state. The resemblance of leukemia to an infectious process and the known action of chemotaxis in infectious leukocytosis suggests, as Reed has observed, that leukemia is due to the action of some chemotactic agent or agents, which, by withdrawing certain varieties of leukocytes from the bone-marrow, cause a compensatory hyperplasia to replace the elements of the type withdrawn. This hypothesis necessarily assumes the existence of different chemotactic agents specific for the different types of leukocytes, an assumption which seems to us perfectly justifiable, if we compare leukemia with infectious processes. As is well known, not all of the chemotactic substances produced in infectious diseases attract the same varieties of leukocytes. That bone-marrow hyperplasia *per se* is incapable of producing the blood picture of leukemia is shown by a number of recorded cases in which this condition existed without the clinical picture of leukemia.

Judging from this case and similar ones in the literature, the changes in the lymphatic apparatus would seem to be entirely secondary, and in the nature of an infiltration with cells derived from the diseased bone-marrow, at times associated with a simple hyperplasia. As has already been stated, there was no evidence in this case, or in similar cases in the literature, of any active formation of mononuclear cells in the lymphatic apparatus, and nothing to lead one to believe that the increase of the mononuclear cells in the blood was due to changes in the lymphatic tissues.

The relation of cases of lymphatic leukemia to so-called pseudo-leukemia has been widely discussed, both by those who uphold the lymph-gland origin of lymphatic leukemia and those who believe in its origin from bone-marrow changes. As far as one can judge from

the literature, it has been taken for granted, almost universally, that pseudoleukemia differs from lymphatic leukemia merely in the absence of the blood changes, the histologic changes in the organs being the same. As Reed points out, the term pseudoleukemia has been used in a very loose fashion, so that it is quite probable that a number of diseases have been grouped under this head. As far as typical Hodgkin's disease is concerned we now know, from Reed's very careful studies, that it presents perfectly definite histologic lesions, which are entirely different from the lesions of lymphatic leukemia, so that the possibility of any relationship between the two diseases is practically excluded. As long as our knowledge of the various conditions classed under the head of pseudoleukemia (Hodgkin's disease excepted) is so imperfect, it would seem impracticable to intelligently discuss the relationship of these cases to true leukemia.

The possible relation of cases of this sort to pernicious anemia was suggested by the clinical appearance and history of our patient, as was the case in one of Pappenheim's patients. The possibility that a preleukemic pernicious anemia can occur in these cases is discussed by Pappenheim in connection with a case reported by Körmoczi in which leukemia was preceded by pernicious anemia. We can see no reason why the two diseases should not follow each other at times merely as a matter of coincidence, but that any causal relationship should exist between the two diseases seems unlikely. In our case, and in the other cases described in the literature, the changes in the spleen, liver, and hemolymph glands which are characteristic of pernicious anemia were not present. As Pappenheim points out, in leukemia we are dealing with a primary specific disease leading to the excessive formation of certain elements of the blood, while in pernicious anemia we are dealing with a non-specific secondary change of a compensatory character.

Finally, we wish to discuss our conclusions as to the deductions to be made from these cases. As far as myelocytic leukemia is concerned there is at present practically a unanimity of opinion that it is due to disease of the bone-marrow. As regards lymphatic leukemia, as already stated, the school of Ehrlich regards it as always primarily a disease of the lymph glands, while the school of Neumann regards it as always primarily a disease of the bone-marrow. We believe that both schools take extreme views. There is good evidence, in our

opinion, that cells of the lymphatic type are formed in normal adults, both in the lymphatic apparatus and the bone-marrow. Theoretically, therefore, it should be possible to have lymphatic leukemia as a result of disease of the lymphatic apparatus, or of the bone-marrow, or of both. In the recent study of the blood and organs of a case of lymphatic leukemia of the ordinary type, we observed that the increase in the leukocytes was for the most part an increase in typical lymphocytes, whereas in the case without enlargement of the lymph glands the increase in leukocytes was in cells differing from the ordinary lymphocyte, as we have described. On the other hand, in the case without enlargement of the lymph nodes there was no evidence of increase in the proper cells of the lymphatic apparatus, while in the typical case of lymphocytic leukemia numerous cells undergoing direct division were to be made out in the lymph nodes. We would, therefore, suggest that while myelocytic leukemia is invariably a disease of the bone-marrow, lymphocytic leukemia may be a disease either of the lymphatic apparatus or the bone-marrow, or both, and we would further express the belief that specific differences exist in the blood picture of the different forms.

A PRELIMINARY NOTE ON SOME EXPERIMENTS TO DETERMINE WHETHER ALCOHOL DOES GOOD IN INFECTIONS BY INCREASING THE BACTERIOLYTIC POWER OF THE BLOOD.

By H. A. HARE, M.D.,
OF PHILADELPHIA.

No one who has given thought to the subject of the treatment of disease can fail to have been impressed with the fact that much of our therapy is based upon empiricism rather than a clear conception of the manner in which certain remedies do good. This is because in many instances we have not a definite conception of the pathologic process underlying the malady or the symptoms which are to be relieved. It is a curious fact that in the only diseases for which specifics have been found we were in one instance, and are in the other instance, ignorant of the cause of the illness, namely, malarial infection and syphilis. A very near associate of quinine and mercury, in so far as their empirical use is concerned, is alcohol in its various medicinal forms, for notwithstanding some differences of opinion it is not to be denied that physicians of experience the world over employ this drug to combat serious infections, and obtain from its use results which cause them to rely upon it when other remedies fail. This is notably the case in the infectious diseases of a febrile type, and peculiarly so in two conditions depending largely upon bacteriemia, septicemia, or the popular blood poisoning, and typhoid fever.

There is not space, even if it were wise, to discuss the very extraordinary divergence of view, or rather antagonism, which exists between experimental investigators on the one hand and clinicians on the other in regard to the effect of alcohol. The one school claims that it is always a depressant poison to all protoplasm in any dose, and that it never acts as a stimulant in the true sense, while the other uses

it with an implicit faith based on bedside experience, shaken a little by the statement of the laboratory worker.

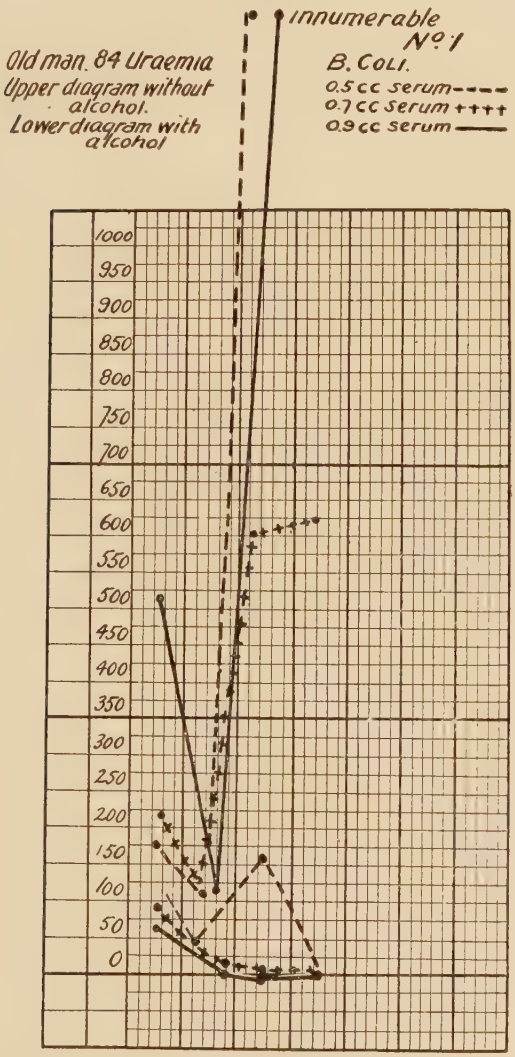
It is incredible that thousands of skilful men should be in error as to the value of alcohol in therapeutics. Some explanation must exist. It has occurred to me that possibly the good might be achieved by the influence of alcohol upon bacteriolysis, and I wish to report at this time a preliminary research which for certain technical and other reasons is as yet imperfect and incomplete. The chief difficulty in making this research an extensive one lay in the fact that I found it almost impossible to find patients whose condition was such that a test of any length could be carried out. Even in so prolonged a disease as typhoid fever there are marked changes in the condition of the patient from week to week, if not from day to day, and therefore it required patients who were suffering from some chronic malady which had impaired their vital resistance, but which did not at the same time progress so rapidly toward death or recovery as to produce striking changes from day to day in the organism. For this reason I place little confidence in the results obtained from examining the blood of typhoid fever patients. In other words, I can be by no means certain that the bacteriolytic increase or decrease does not depend more upon the natural history of the disease than upon the effect of alcohol. The results, however, obtained in some of the cases of typhoid fever are of interest in that they correspond to those obtained in the other cases which I am about to cite, in which the patients suffered from chronic affections varying but little from day to day and week to week. In other cases of enteric fever the results were so manifestly produced by changes in the disease that they are not cited.

The first case was that of an old man, aged eighty-four years, suffering from chronic renal disease and marked uremia of a subacute type, in whom the administration of alcohol seemed to produce a distinct increase in bacteriolytic power. His blood was tested on October 29th, having been taken on the 28th. He was given eight ounces of whiskey on each of the next succeeding five days, the blood being tested at the end of that period while the alcohol was still being taken.

The results obtained when 0.9 cubic centimeter of blood was used before alcohol showed immediately 516 colon bacilli, at the end of four hours 111, and in twelve hours they were innumerable; whereas after

the alcohol had been taken examination showed immediately 76 bacilli, and after that the plate was sterile.

CHART 1.



Somewhat similar results were obtained with 0.7 and with 0.5 cubic centimeter of serum, but smaller quantities failed to destroy the colon bacillus after alcohol was used.

The results are well shown in Chart 1, the details of which are to be found in the accompanying table:

Before alcohol.

	Immediate.	4 hours.	12 hours.	24 hours.
Control	73	61	Innumerable.	Innumerable.
0.1 c.c. blood	32	62	1,433	Innumerable.
0.3 c.c. blood	39	49	53	256
0.5 c.c. blood	184	120	Innumerable.	Innumerable.
0.7 c.c. blood	220	132	608	620
0.9 c.c. blood	516	111	Innumerable.	Innumerable.

After alcohol.

	Immediate.	4 hours.	12 hours.	24 hours.
Control	364	6	Innumerable.	Innumerable.
0.1 c.c. blood	195	134	1,417	Innumerable.
0.3 c.c. blood	99	74	44	185
0.5 c.c. blood	94	49	162	10
0.7 c.c. blood	60	17	Sterile.	Sterile.
0.9 c.c. blood	58	Sterile.	Sterile.	Sterile.

The results obtained with the bacillus typhi, used simultaneously, are not quoted because the blood at all times killed all of them. This experiment was made during preliminary tests and while searching for a more accurate process. It is quoted only because it is in accord with those in which more accuracy was possible, and so is in the nature of a confirmation of the experiments about to be described, which, I am free to confess, are so decisive that had I not perfect confidence in the technic, combined with the fact that the bacteriologist did not know what blood was being worked with, I would be inclined to suspect an error. The possibility of error was further avoided by having several persons make the count.

The second patient was one suffering from chronic tuberculous infection of the lungs, bowels, and peritoneum, of that slow, chronic type which gets worse so gradually that the difference can scarcely be noted from week to week, although the malady was so severe that the patient was emaciated to the last degree and had lost all control of the anal sphincter.

The method of experimentation, so far as the bacteriologic research was concerned, was as follows:

The clear serum was removed from the clot by means of a sterile graduated pipette, and portions of 0.1, 0.3, and 0.5 cubic centimeter transferred directly to small test tubes in which had been placed 0.9, 0.7, and 0.5 cubic centimeter, respectively, of physiologic salt solution and also three drops of bouillon.

The inoculations were made from suspensions in physiologic salt solution of B. coli and B. typhosus, the organism for these suspensions being taken from eighteen-hour-old agar slants. The suspensions were so made that they held about 50,000 organisms to the *oese*, a condition which, after some experimentation, was determined by the degree of opacity of the liquid. These suspensions were allowed to stand for one-half hour to permit dead organisms and clumps to fall to the bottom.

Six loopfuls of the inoculating material were transferred to each portion of serum to be tested, from which three loopfuls were immediately plated on nutrient agar. The tubes were then placed in an incubator at 37° C., and at intervals of one, three, five, and twenty-four hours series of plates were made, using three loopfuls for each. These were counted when from eighteen to twenty-four hours old. The "controls" mentioned were six loopfuls of suspension in one cubic centimeter of physiologic salt with three drops of bouillon. The "suspensions" consisted of one loopful of the organisms suspended in the salt solution, transferred to an agar tube, and immediately plated.

It will be observed that, accepting the suspension as 50,000 per *oese*, each experimental tube was supplied with approximately 300,000 organisms.

The colon and typhoid bacillus were employed to check one another. It was found that in nearly every case the bacteriolytic power of the blood was sufficient to destroy the typhoid bacillus, even if alcohol were not employed. This was not true of the colon bacillus, which is very much more tenacious of life, and the results which are stated below are based upon the bacteriolytic power of the blood upon the colon bacillus. The results, I think, show clearly that alcohol increases the bacteriolytic power of the blood when given in ordinary medicinal doses, at least in certain cases, and that this increase in bacteriolytic power is in direct ratio to the size of the dose, both in rapidity and degree.

The charts of this experiment follow, and the detailed tables from which they are made are appended.

When the alcohol was first begun and given in very small doses, as stated below, the bateriolytic power was very poor. When the dose was gradually increased the bacteriolytic power also increased, and

when the alcohol was stopped it fell again. When the alcohol was renewed it rose again (see Chart 2*b*).

Alcohol, half-ounce (15 c.c.) t. i. d. (45 c.c. a day) from January 18th to 22d.

Blood drawn January 22, 4 P.M.; received January 23, 1903, 9.30 AM. Used 11 A.M., January 23.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension	67,400				
Control	780	1,362	9,166	Innumerable.	Innumerable.
0.1 c.c. serum	540	187	359	2.849	Innumerable.
0.3 c.c. serum	499	55	332	2,542	Innumerable.
0.5 c.c. serum	608	39	192	1,801	Innumerable.

Alcohol, half-ounce (15 c.c.) every four hours (90 c.c.) from January 22d to January 28th.

Blood drawn January 28; received January 29, A.M. Used 11.30 A.M., January 29.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension	60,336				
Control	821	1,274	16,236	Innumerable.	Innumerable.
0.1 c.c. serum	737	156	172	45	Innumerable.
0.3 c.c. serum	712	75	34	32	12,300
0.5 c.c. serum	729	9	21	19	8,544

Alcohol, 5 drachms (20 c.c.) every three hours (150+ c.c. a day) from January 29th to February 3d, and 6 drachms (24 c.c.) every three hours (190 c.c.) from February 3d to February 10th.

Blood drawn February 10 at 4 P.M.; used February 11 at 11 A.M.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension	54,500				
Control	327	457	520	707	Innumerable.
0.1 c.c. serum	670	241	36	10	Sterile.
0.3 c.c. serum	592	198	12	3	Sterile.
0.5 c.c. serum	324	144	5	5	Sterile.

Alcohol, 6 drachms (24 c.c.) every three hours (190 c.c.) from February 10th to 13th, and 3 drachms (12 c.c.) every three hours (96 c.c.) from 13th to 15th, but no alcohol had been given for two days at time of drawing blood.

Blood drawn February 17. Received February 18; used at 11 A.M.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension	33,500				
Control	700	862	1,513	22,144	
0.1 c.c. serum	252	4	0	0	
0.3 c.c. serum	89	0	0	0	
0.5 c.c. serum	30	0	0	0	

No alcohol for ten days.

Blood drawn February 25. Received February 26; used 12 M.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension	71,040				
Control	9,360	1,051	3,420	45,360	Innumerable.
0.1 c.c. serum	1,245	833	982	20,027	Innumerable.
0.3 c.c. serum	1,219	301	171	381	Innumerable.
0.5 c.c. serum	1,047	286	18	104	40,200

Alcohol for six days. Six drachms (24 c.c.) every three hours (190 c.c. a day).

Blood drawn March 15, 4 P.M.; used March 16, 4 P.M.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension . . .	46,900				
0.3 c.c. serum . .	360	116	37	14	Sterile.

The third experiment that I desire to report was also made in a case of advanced peritoneal tuberculosis with pulmonary lesions. The same methods were employed and the following results obtained (see Chart 3*a* and 3*b*) which, while they are not so striking as they were in Experiment No. 2, are distinctly confirmatory of it. Thus it will be seen that when no alcohol was given the organisms were innumerable in twenty-four hours, whereas when alcohol was administered, at the end of twenty-four hours they numbered only 1300 if the dose was small, and 18,200 if it was larger. When the alcohol was stopped they became innumerable again at the end of twenty-four hours.

This held true when either 0.3 or 0.5 cubic centimeter of serum was used. The smaller quantities of serum were too feeble to produce any effect.

No details of the tests with the bacillus typhosus are given, as they were destroyed by the serum in all tests at once.

I also carried out the following experiments in a case of typhoid fever with the colon and typhoid bacillus, but the typhoid bacillus was again at once destroyed in both experiments. At the time they were made the skill in technic had not been attained by long practice, as is shown in the different suspension counts. This record is therefore presented only as being of some collateral interest. It may be urged in this case that the progress of the disease was the cause of the diminished bacteriolytic power, since the low bacteriolytic effect was in the third week, whereas the high effect with alcohol was in the second week.

No alcohol whatever.

Blood drawn March 25, 4 P.M. Received March 26; used 11 A.M.

B. Coli.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension . . .	50,500				
Control . . .	774	752	5,453	33,517	Innumerable.
0.1 c.c. serum . .	779	397	392	1,706	Innumerable.
0.3 c.c. serum . .	662	297	75	70	Innumerable.
0.5 c.c. serum . .	630	398	15	14	Innumerable.

Alcohol, 4 drachms (16 c.c.) every four hours, 3 ounces (96 c.c) a day, from March 25th to March 30th.

Blood drawn March 30. Received March 31, 1903; used 11 A.M.

B. Coli.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension . . .	56,300				
Control with no serum	930	1,030	15,020	Innumerable.	Innumerable.
0.1 c.c. serum . .	1,020	200	150	52	Innumerable.
0.3 c.c. serum . .	1,002	102	87	40	1,300
0.5 c.c. serum . .	700	50	20	15	8,420

Alcohol, half an ounce every three hours (15 c.c.), 4 ounces (124 c.c.) a day, from March 30th to April 7th.

Blood drawn April 7. Received April 8, 9 A.M.; used 12.15 P.M.

B. Coli.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension . . .	49,800				
Control . . .	1,340	1,113	1,854	16,504	Innumerable.
0.1 c.c. serum . .	1,001	989	1,150	413	Innumerable.
0.3 c.c. serum . .	1,123	879	427	210	18,200
0.5 c.c. serum . .	959	789	413	129	5,421

Alcohol stopped for one week.

Blood drawn April 14. Received April 15, 1903, 9 A.M.; used 11.30 A.M. Fourth test.

B. Coli.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours
Suspension . . .	75,000				
Control . . .	3,630	1,383	18,172	Innumerable.	Innumerable
0.1 c.c. serum . .	752	1,409	1,510	1,564	Innumerable.
0.3 c.c. serum . .	2,347	1,908	1,192	787	Innumerable.
0.5 c.c. serum . .	2,294	1,193	692	365	Innumerable.

Male, aged twenty-six years. Typhoid fever. Alcohol was given during the second week in the dose of about 10 drachms a day.

Immediately after the exposure to 0.5 cubic centimeter of the serum the number of colon bacilli equalled 2059; in one hour, 514; in three hours the plate was sterile, and remained so at the end of the third, fifth, and twenty-fourth hours; whereas, when alcohol was stopped, and the blood was tested one week later, being the third week of the disease, the following results were obtained with the colon bacillus: Immediately after the bacillus numbered 943, in one hour 168, in three hours 20, in five hours 4, and at the end of twenty-four hours they were innumerable, instead of being entirely destroyed as when alcohol was used. This effect did not take place when 0.3 cubic centimeter of serum was used, the two curves being about equal. These results are shown in Charts 4*a* and 4*b*.

The details of the count in this case follow:

Alcohol, 10 drachms (40 c.c.) a day.

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension . . .	202,560				
Control . . .	3,296	2,724	10,383	Innumerable.	Innumerable.
0.05 c.c. serum . .	9,579	1,860	598	371	Innumerable.
0.1 c.c. serum . .	6,238	1,441	190	38	Innumerable.
0.3 c.c. serum . .	2,766	880	9	2	Innumerable.
0.5 c.c. serum . .	2,059	514	Sterile.	Sterile.	Sterile.

No alcohol.[1]

Colon.	Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension	71,608				
Control	1,176	7,388	Innumerable.	Innumerable.	Innumerable.
0.1 c.c. serum	1,229	249	129	55	Innumerable.
0.3 c.c. serum	1,031	200	85	14	Innumerable.
0.5 c.c. serum	943	168	20	4	Innumerable.

The interesting question arises as to whether the increase in bacteriolytic power when 0.5 cubic centimeter was used depended upon an influence exercised upon the complemental body. The following experiments with this end in view were performed.

The study of the relative amount of complement was made by adding definite quantities of fresh, unheated serum to measured quantities of serum which had been heated for one hour at 56° to 68° C. Each mixture was then made up to one cubic centimeter with sterile physiologic salt, inoculated from the suspension as above described and plated. Complement tests were not attempted in Cases 1 and 4. Unfortunately the serum for the second half of the complement test in Case 2 was lost through the breaking of the tube containing it. The following record as to the complement therefore deals with the serum from Case 3.

Before alcohol.

Complement test with *B. Typhosus.*
Blood drawn March 25; used March 26.

		Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension		55,500				
Control of whole serum 0.3 c.c.+ physiologic salt solution to make 1 c.c.		702	12	Sterile.	Sterile.	
Heated serum.	Unheated serum to reactivate.					
0.3 c.c.	2.5 per cent.	1,030	400	105	15	10,700
0.3 c.c.	5 per cent.	1,020	52	Sterile.	Sterile.	

Alcohol, 4 drachms (16 c.c) every 4 hours, 3 ounces (96 c.c.) a day.

Blood drawn March 30, at 10 P.M.; used March 31, 11 A.M.

Heated serum.	Unheated serum to reactivate.					
0.3 c.c.	2.5 per cent.	2,522	270	16	2	720
0.3 c.c.	5 per cent.	1,706	65	0	0	Sterile.
0.3 c.c.—as control complement is removed.		1,906	1,309	1,835	1,936	Innumerable.

[1] The non-alcohol record follows that with alcohol, because in this case it was alcohol first, and no alcohol afterward.

Alcohol increased to 4 ounces (125 c.c.) every twenty-four hours.

Heated serum.	Unheated serum.					
0.3 c.c.	2.5 per cent.	1,200	1,044	134	14	1,002
0.3 c.c.	5 per cent.	1,030	742	25	2	0

Alcohol stopped for one week.

Blood drawn April 14. Received April 15, 1903, 9 A.M.; used 11.30 A.M.

B. Typhosus.		At once.	1 hour.	3 hours.	5 hours.	24 hours.
Heated serum.	Unheated serum.					
0.3 c.c.	2.5 per cent.	1,680	2,236	689	371	Innumerable.
0.3 c.c.	5 per cent.	2,653	2,210	164	88	10,490

With the bacillus coli in the complement experiments in Case 4 the following results were obtained:

Before alcohol.

Complement test with bacillus coli. Blood of March 26.

		Immediate.	1 hour.	3 hours.	5 hours.	24 hours.
Suspension		50,500				
Heated serum.	Unheated serum.					
0.3 c.c.	60 per cent.[1]	920	214	50	10	Innumerable.
0.3 c.c.	80 per cent.	700	173	60	4	Sterile.

Alcohol, 4 ounces (125 c.c.) a day.[2]

Blood of April 7; used April 8.

Heated serum.	Unheated serum.					
0.3 c.c.	60 per cent.	1,033	1,409	90	760	21,300
0.3 c.c.	80 per cent.	1,066	1,256	13	429	710

Alcohol stopped for one week.

Blood drawn April 14. Received April 15, 1903, 9 A.M.; used 11.30 A.M.

Complemental test. *B. Coli.*						
Heated serum.	Unheated serum.	At once.	1 hour.	3 hours.	5 hours.	24 hours.
0.3 c.c.	60 per cent.	1,971	1,722	689	8,904	Innumerable.
0.3 c.c.	80 per cent.	2,517	1,604	570	2,577	Innumerable.

This chart (No. 5*a*) shows the results reached with the bacillus typhosus when 3 cubic centimeters of heated serum were reactivated by 2.5 per cent. of unheated serum. A chart of the effect of 5 per cent. is not shown, as that quantity is so powerful as to kill all the B. typhi in all tests.

The activity of the complement of the serum upon the bacillus typhosus after alcohol when 2.5 per cent. of unheated serum was used to reactivate was greater than it was during the time before alcohol was given and after alcohol was stopped. When the bacillus typhosus was exposed to serum reactivated by 5 per cent. of unheated

[1] This per cent. is based on Longcope's quantities.

[2] No complement test with the bacillus coli of the blood of March 30 is given because of an accident which destroyed the plates.

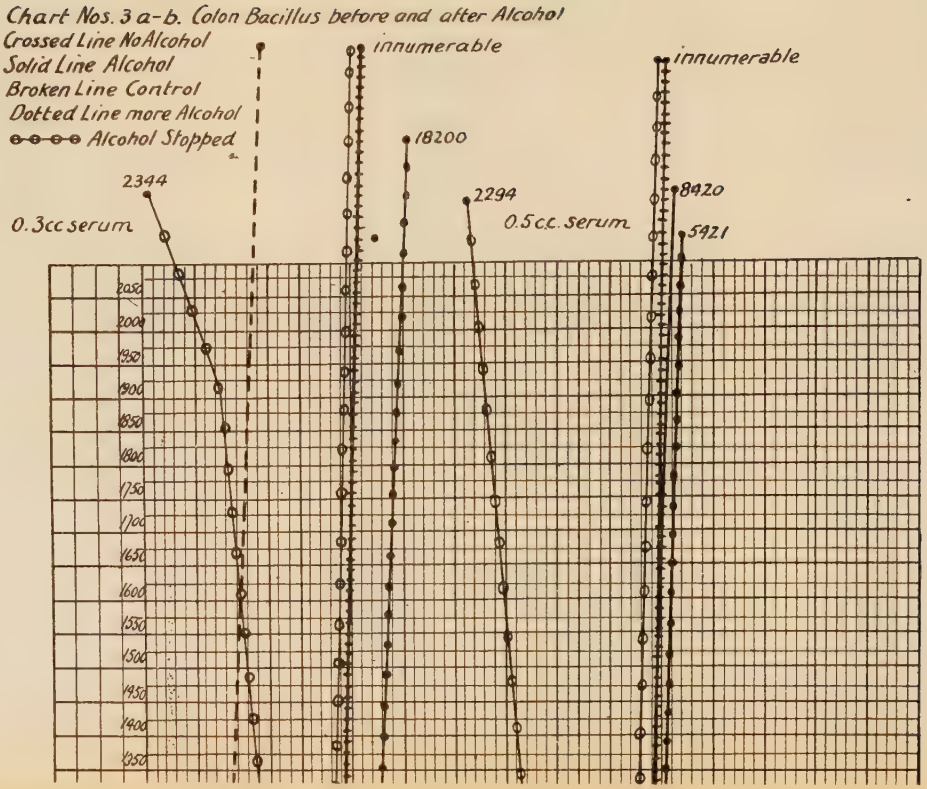


Chart Nos. 3 a-b. Colon Bacillus before and after Alcohol
Crossed Line No Alcohol
Solid Line Alcohol
Broken Line Control
Dotted Line more Alcohol
Alcohol Stopped
innumerable
innumerable
18200
2344
2294
8420
0.3cc serum
0.5cc. serum
5421
2050
2000
1950
1900
1850
1800
1750
1700
1650
1600
1550
1500
1450
1400
1350

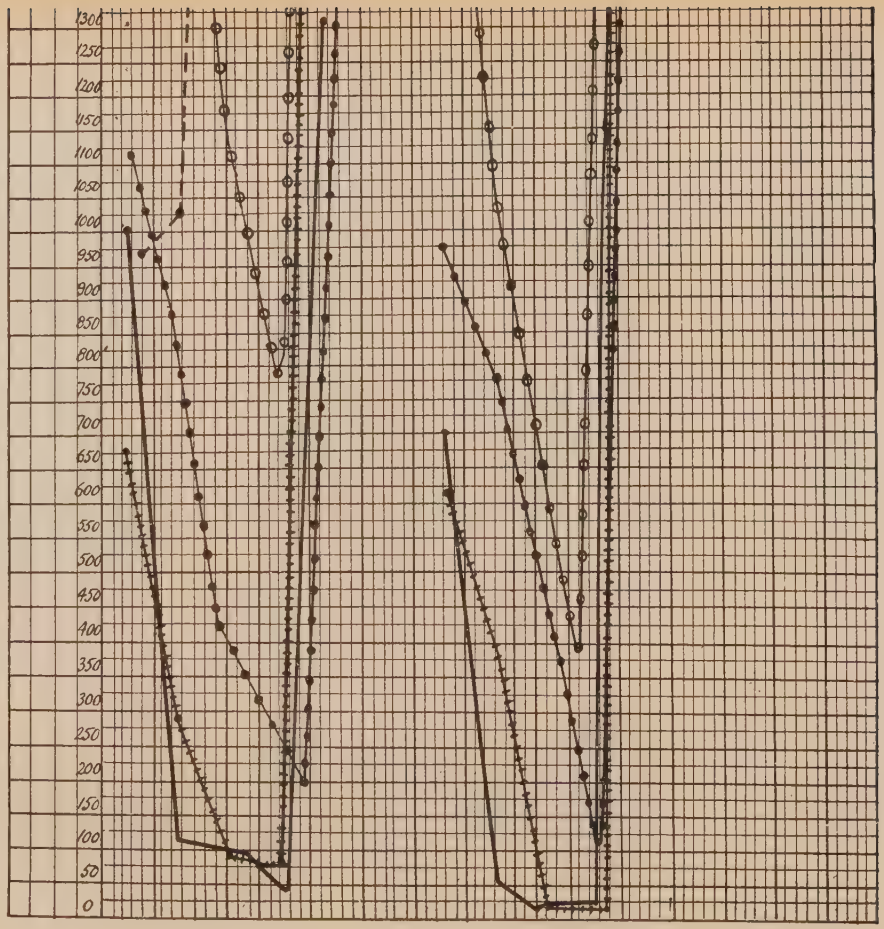

1300
1250
1200
1150
1100
1050
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0

Chart No. 5 a. Complement Experiment
Bacillus Typhosus with heated and unheated serum.
before and after Alcohol.
Crossed Line no Alcohol
Solid Line Alcohol.
Dotted Line, more Alcohol.
— — — Complement destroyed
●●●● Alcohol stopped

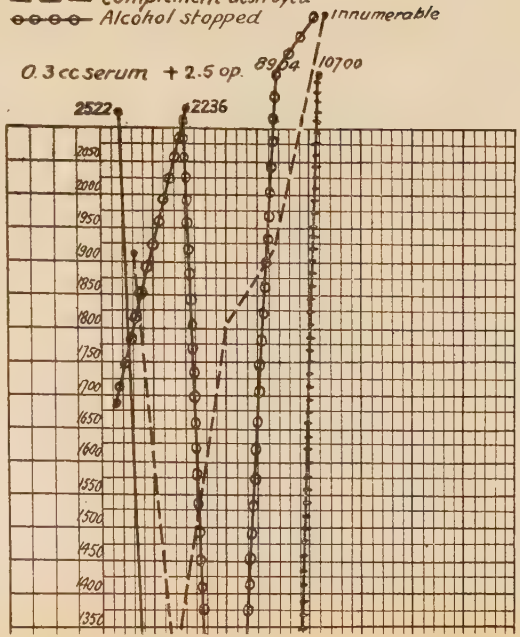
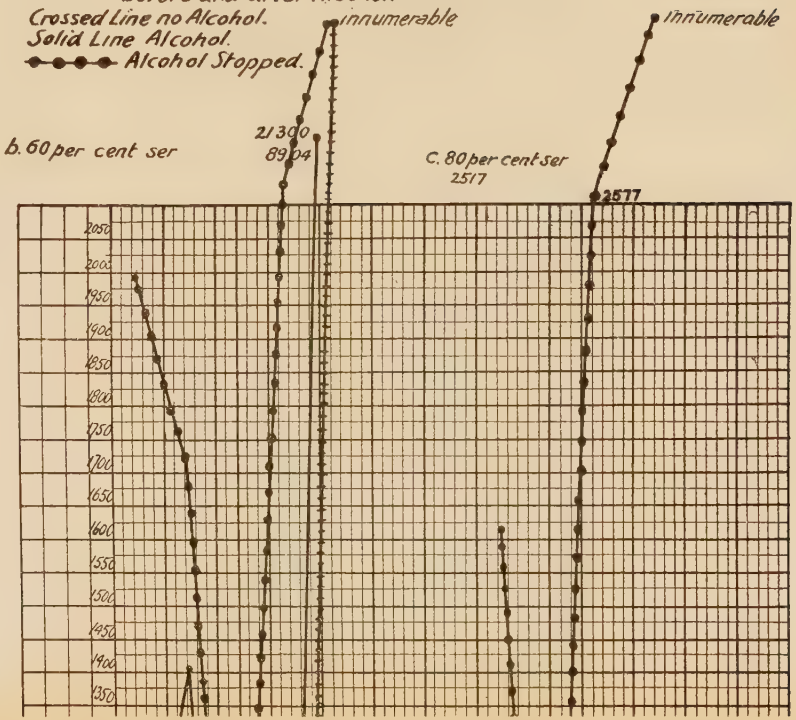
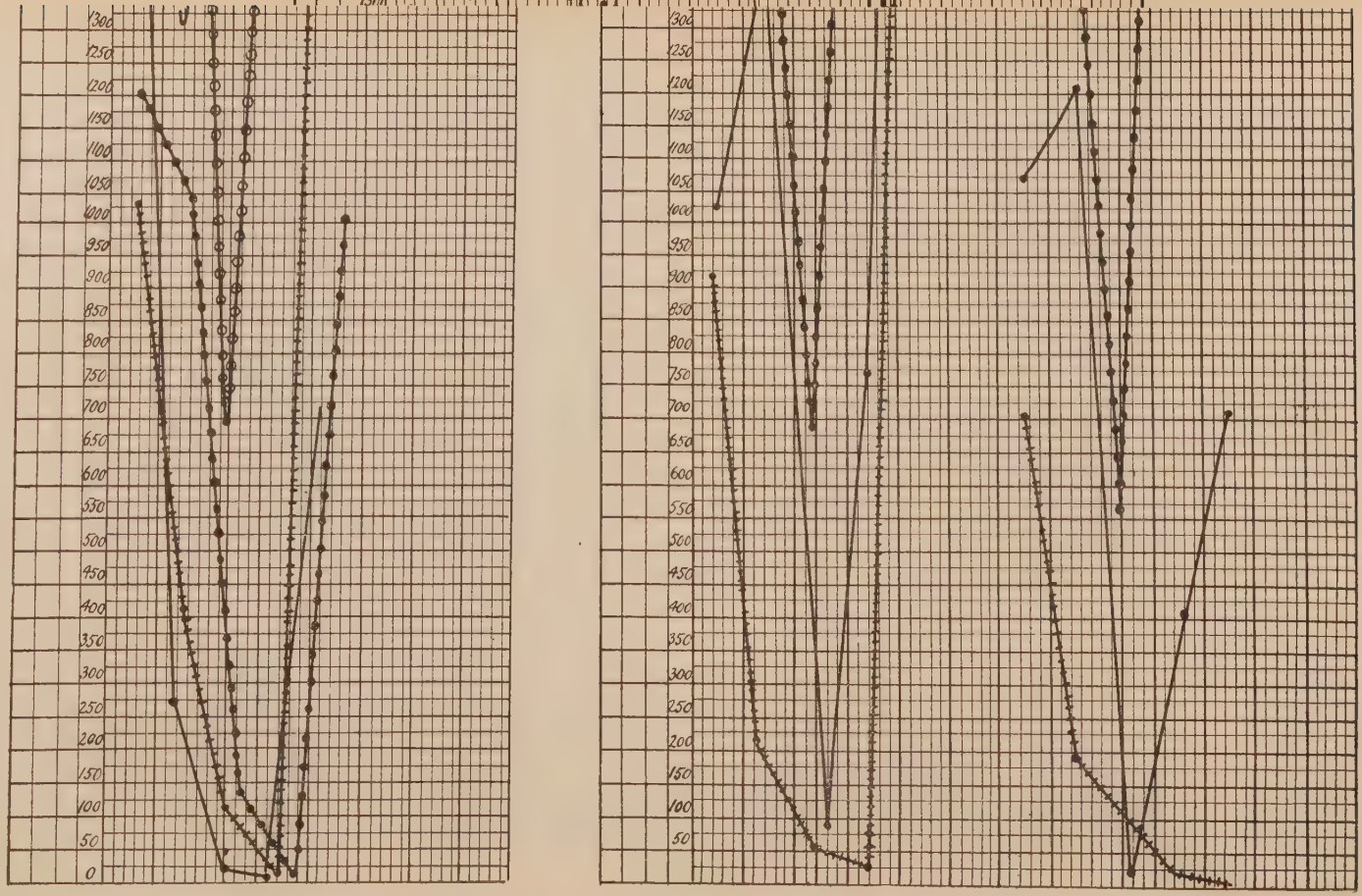


Chart 5 b-c Complement Experiment
Bacillus Coli with heated and unheated serum.
before and after Alcohol.
Crossed Line no Alcohol.
Solid Line Alcohol.
●●●● Alcohol Stopped.




1300
1250
1200
1150
1100
1050
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0

serum, it destroyed the micro-organisms speedily in all the experiments except the last, in which they multiplied enormously. It is to be noted that in the ordinary experiments to determine the bacteriolytic influence of the serum upon the bacillus typhosus, the serum in all cases so speedily destroyed these micro-organisms before alcohol was given, during its administration, and after it was stopped that it has not been thought worth while to embody these results in this paper; yet in the tests to determine the effect on complement, the same high grade of bacteriolytic influence was not manifested. Whether the practically uncontrolled multiplication of the organisms which took place in the last experiment to determine the influence of the complement indicates that the serum, through the progress of the disease or the lack of alcohol, had lost its bacteriolytic power, or whether this great increase was due to an error in technic or in counting, is difficult to determine.

When the bacillus coli was used with 60 per cent. of unheated serum to reactivate, the bacteriolytic power was greater when alcohol was used than before it was given and after it was stopped. When 80 per cent. unheated serum was used with the bacillus coli, the bacteriolytic power was best before alcohol, next with alcohol, and poorest when alcohol had been stopped for a week. Here, again, it is difficult to determine whether the low bacteriolytic power of the reactivated serum was due to impaired complemental activity or to an error in technic. That it is the latter is pointed to by the fact that in the experiments to determine bacteriolysis alone the bacteriolytic power was greater when alcohol was given than when no alcohol was used.

1. The conclusions to be reached from this research are that the use of alcohol seems to have the power of combating infectious diseases by increasing the bacteria-destroying power of the blood.

2. While the experiments so far made are too few and too contradictory to determine the question, they indicate so far as they have gone that this effect is produced to some extent at least by an increase in complement.

I desire to thank Miss M. E. Pennington for the care she has exercised and interest she has shown in carrying out the bacteriologic details of this research. Her skill has still further convinced me of the accuracy of the work done in the Philadelphia Clinical Laboratory, which is under her direction and control.

STUDIES ON THE ACTION OF ALCOHOL IN DISEASE, ESPECIALLY UPON THE CIRCULATION.

By RICHARD C. CABOT, M.D.,
OF BOSTON.

Perhaps no subject has been more frequently or more heatedly discussed during the last few years than the action and value of alcohol. We have had two interesting symposia upon the subject in Boston within a year, and many similar discussions are reported in domestic and foreign journals. One might think, therefore, that the subject was about threshed out, and that nothing new could be said about it; but as one looks over the reports of these discussions one fact is very striking, and that is the scarcity of experimental evidence regarding the action of alcohol in diseased human beings.

In the discussions to which I have referred the disputants have usually ranged themselves in two parties: those favoring the use of alcohol on one side and those opposed to its use on the other. Those who favor its use usually do so on the ground of their general impression that it has done good in cases under their observation; those opposed to the use of alcohol usually refer to a number of experiments, for the most part not very recent ones, upon the action of the drug in the lower animals; but very rarely has anyone anything to say about experiments or measurements of the action of the drug upon any of the functions of the diseased human being. The "advocates of alcohol" say that it does good, but if you ask them *what* good does it do? Does it decrease temperature? does it improve sleep? does it slow or strengthen the heart's action, and, if so, how much? they have rarely anything to answer. On the other hand, if you ask the "opponents of alcohol" what harm it does they will point to the effect produced on a dog or a rabbit by doses of alcohol which would correspond to giving a man a quart of whiskey at a drink, or they will refer you to experiments on healthy soldiers or typesetters. The use of such evidence assumes that alcohol acts in the same way in all

animals, whereas we know well that its action in mammals is very different from its action in birds, and have by no means proved that what is true of its action in dogs or rabbits is true of its use in man. Another common assumption is that the effects of alcohol in disease are similar to its effects in health; but this is a totally unproved assumption, and there is, I think, a good deal of evidence that it is not true.

It seems to me, therefore, that there is a real need for exact, experimental evidence regarding the action of alcohol in sickness, and it is to this problem that I have addressed myself. I have not sought to show that alcohol does good or that it does harm. I have rather tried to find out *what it does:* what its effect is upon temperature, upon the heart and pulse, upon the rapidity of the respiration, upon the amount of urine, upon the sweat, upon the appearance of the tongue, upon the appetite, and upon the cerebral condition of the patient as shown in the amount he sleeps, in the effect of the drug upon delirium, and upon his spirits so far as could be ascertained by talking with him.

I will not deny that I have approached the subject with a marked bias, but I hasten to add that I have done all I could to prevent this bias from influencing my observations; that I have succeeded, at least to some extent, is evidenced, I think, by the fact that my results have not come out at all as I expected and, indeed, hoped that they would.

In order to counteract so far as possible the bad effects of my prejudices, I have recorded each of my observations on separate slips of paper without allowing myself to refer to the chart in which they were later recorded. As I could not retain in memory the records of the individual patients, and did not allow myself to be reminded of them by looking at the chart, I was thus unable to influence the readings in the direction of my expectations, as I previously found it very tempting to do. In the study of the effects of alcohol on temperature, appetite, sleep, etc., I have circumvented my bias by getting nurses, who had no idea of what I had in mind, to record the data for me on blanks provided for the purpose.

I have said that there was a dearth of experimental evidence regarding the action of alcohol in diseased persons, but this lack is much more striking in certain directions than in others. Certain points have, I think, been pretty well cleared up, while others are

still obscure; hence it may not be out of place to sum up what may be regarded as relatively settled, in order that the unexplored regions may be made more evident by contrast.

About the food value and the digestive action of alcohol, about its effect on temperature, respiration, and secretions, and the susceptibility of the lower animals to infection, there is a good deal that we may consider settled.

On the other hand, there are very few experiments upon its action on the *circulation* of the sick or upon the protective powers of the human blood against infection.

These two problems, then, confront us:

1. What effect has alcohol upon the circulation in sick persons?

2. What is its effect on the power of man's blood to protect his organism against infection?

The first of these two questions I have tried to answer in the present lecture. The second I hope to attack later.

Before presenting the results of my own experiments I will endeavor to summarize what seems to me established as the result of work previous to my own.

We may treat as established the following statements:

Alcohol and Metabolism.

1. In healthy persons alcohol is capable of replacing, satisfactorily, the fats and carbohydrates of ordinary food.

2. It is not yet settled whether or not alcohol can replace the proteids of our customary diet.

3. The food value of alcohol as a substitute for carbohydrates and fat is perfectly consistent with its toxic properties. It is beyond doubt both a food and a poison.

The Action of Alcohol on Digestion and Absorption.

4. While in the stomach alcohol disturbs the digestive processes to a greater or less extent, according to its concentration.

After absorption (either from the stomach or from the intestine) alcohol acts upon the stomach through the nervous system, and exerts a favorable influence both on its secretions and on its motility; but the nervous system is soon blunted to its influence, so that more and more is needed to influence digestion.

5. On the intestinal absorption of food alcohol has no considerable influence, so far as is known.

Alcohol and Diuresis.

6. In healthy persons and in renal or cardiac disease alcohol has no considerable effect as a diuretic. The free diuresis often seen after beer-drinking is due in part to the water ingested and in part to the CO_2 and other non-alcoholic constituents of the beer.

Alcohol and Diaphoresis.

7. The experimental data are not conclusive and great individual differences exist, but the majority of experiments seem to show that alcohol diminishes sweating in healthy persons.

Alcohol and Respiration.

8. Practically all experiments show that under the influence of alcohol a larger volume of air passes through the lungs. This is especially marked in fatigued persons. There is, however, no increase in the amount of O_2 absorbed or in the amount of CO_2 given off.

The patient is made to do more work in breathing without getting any known benefit from it.

Alcohol and Pulse Rate.

Lichtenfels and Frohlich[1] found first a decrease, later an increase in pulse rate.

Tscheschichin[2] and Ruge[3] noted a very marked rise in pulse.

Zimmerberg[4] could find no variation from normal. Reiss got similar results.

Mertens[5] noted no change; Martins[6] a decrease; Jacobi,[7] Duchek,[8] and Hemmeter[9] noted no increase.

[1] Lichtenfels and Frohlich. Mathemat. naturwissenschaft Klin., Band iii. p. 113.
[2] Tscheschichin. Dubois' Arch. f. Anat. und Physiol., 1866, p. 151.
[3] Ruge. Virchow's Archiv, 1870, vol. xlix.
[4] Zimmerberg. Dissert. Dorpat, 1869.
[5] Mertens. Arch. de Pharmacodynam., 1896, vol ii. p. 157.
[6] Martins. Deutsche Klinik, 1855, No. 44.
[7] Jacobi. Ibid., 1857, 22, 31, 34, iii.
[8] Duchek. Prager Vierteljabrschr., 1853, vol. iii. p. 104.
[9] Hemmeter. Transactions of the Medical Faculty of Baltimore, 1889.

In all the experiments in which subjects have been put into an unchanging environment and conditions, the changes in pulse before and after alcohol sink to a minimum.

Wendelstadt took special pains that the persons on whom he experimented should remain quiet some time before the beginning of the test, and stay in just the same position after swallowing the alcohol. With these precautions the changes in pulse rate were trifling. For a few beats the pulse rate sometimes rose a little, but soon returned to normal. Occasionally there was a slight decrease in rate. The following data may be quoted:

N. K., healthy, fasting, horizontal position for two hours before the experiment.

1.

9.30 A.M.	Pulse	54
9.50 "	"	56
10.07 "	Sherry	300 c.c. (= 10 ℥).
10.15 "	Pulse	56
10.40 "	"	56
11.05 "	"	56

2. Same subject: same conditions.

8.55 A.M.	Pulse	60
9.15 "	"	60
9.30 "	Brandy	100 c.c. (3½ ℥).
9.40 "	Pulse	57
10.00 "	"	58
10.20 "	"	58
10.40 "	"	55
11.00 "	"	60

3. Same subject after a hard day's work and one-half hour in horizontal position.

6.40 P.M.	Pulse	64
6.55 "	Absolute alcohol, 2 ℥ (diluted).	
7.05 "	Pulse	64 (subject drunk).
7.28 "	"	64
7.55 "	"	68
8.15 "	"	64 (less drunk).
8.35 "	"	68

To the finger the pulse, after alcohol, feels fuller and stronger, and the sphygmograph shows a tracing like the "pulsus celer" of aortic regurgitation.

Blood Pressure after Alcohol.

Zimmerberg[1] found, after putting alcohol into a cat's stomach, a marked fall in blood pressure.

Gutnikow[2] experimented on curarized dogs into whose stomachs he

[1] Loc. cit.

[2] 2 Ext. f. klin. Med., 1892, vol. xxi. p. 128.

introduced 250 c.c. of 50 per cent. alcohol. The result was a considerable fall in blood pressure, together with a dilatation of the small arteries, capillaries, especially in the territory of the splanchnic.

The dog here used was so small (20 kilos) and the dose so enormous that no inferenee ought to be made from these experiments as to the effect of moderate doses in man.

Weissenfeld[1] reports work done in Binz's laboratory. The experiments were carried out on men with the help of v. Basch's sphygmomanometer. After two or three ounces of sherry, the pulse rose in three cases from 15 to 30 mm. Hg; in one even as much as 60 mm. Hg.

Schule,[2] working with Gaertner's tonometer on a healthy man, recorded a fall from 110 to 95 mm. Hg twenty minutes after sherry and brandy. An hour later the pressure was 115 again.

Rosenfeld[3] worked with dogs, connecting the femoral artery with a mercury manometer. He was careful to avoid the common mistakes of overdosage and overconcentration in the alcoholic solutions used, which were of 10 to 25 per cent. strength, and introduced by a tube into the dog's stomach.

The question whether dogs tolerate alcohol better than men seems to be answered in part by the following facts:

1. It takes the same dose per kilo to narcotize an average man or an average dog.

2. It takes, approximately, the same dose per kilo to kill a man or a dog.

But to make sure that he did not err on the side of too small dosage, Rosenfeld increased his doses from the equivalent of one ounce of whiskey at a time up to the equivalent of ten ounces of whiskey.

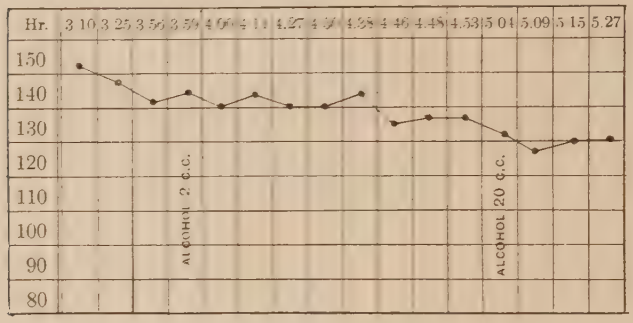
The upshot of his 300 or more measurements in eight dogs is that alcohol has no appreciable effect upon the dog's blood pressure. He used fresh dogs with high blood pressure (152 mm. Hg), tired dogs with low pressure (82 mm. Hg), and dogs with pressures intermediate.

The result was the same in all cases. Variations in the pressure

[1] Pflüger's Archiv, vol. lxxi.
[2] Berliner klin. Wochenschrift, 1900, No. 33.
[3] Der Einfluss des Alcohols auf den Organism, Weisbaden, 1901.

from hour to hour was no greater than occurred spontaneously—*i. e.*, when no alcohol was given. (See charts.)

CHART 1.



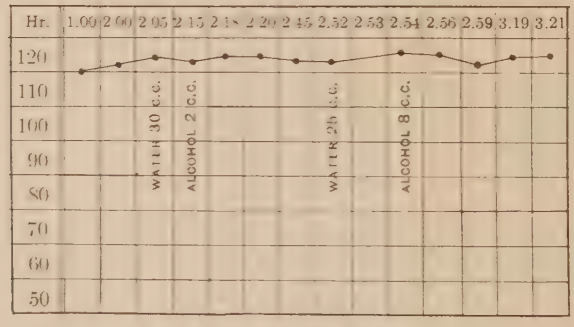
Dog 1. Pressures in Hg mm.

2 c.c. of alcohol at a dose for a dog of 8 kilos, corresponding to a little over one ounce of whiskey for an adult.

Alcohol and Temperature.

In states of profound intoxication, belonging, practically, to the class of collapse states, there may be a very marked lowering of tem-

CHART 2.



Dog 2. Pressures in Hg mm.

perature. Experimentally, Rosenfeld produced readings at 88.7 F. in dogs.

Therapeutic doses of alcohol given to sound men seem to produce a slight lowering, amounting, according to the experiments of Binz's

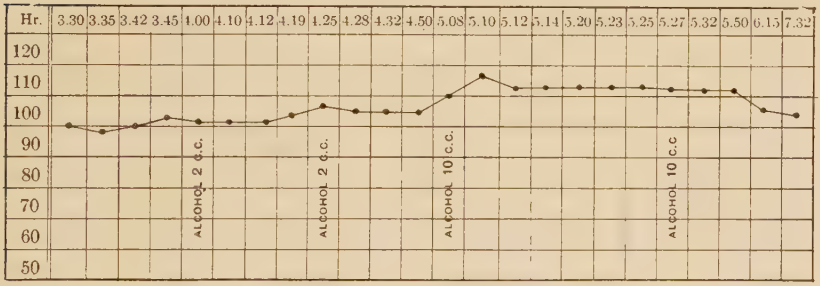
pupils, to about 0.7 of a degree Fahrenheit. In sick people the decrease was about the same. The temperature of the skin is greater than that of the rectum, a fact which seems to indicate that the lowering of the rectal temperature and presumably of that of the internal organs in general is due to the dilatation of the cutaneous vessels.

Dumouly[1] found that no effect was produced in fever patients by doses of less than twenty grams of absolute alcohol (= about $1\frac{1}{2}$ ounces of whiskey.

Alcohol and the Neuromuscular System.

The most recent and careful researches on this much-disputed point seem to show that in fresh, healthy men the power of volun-

CHART 3.



Dog 3. Pressures in Hg mm.

tary muscular movement is increased about 7 per cent. for the first half-hour, after which there is decrease to a point about 5 per cent. below the normal.

By diminishing the sense of fatigue alcohol undoubtedly enables men to push themselves for a short time beyond the limit which nature would otherwise have imposed upon them through fatigue.

Alcohol and the Susceptibility to Infection.

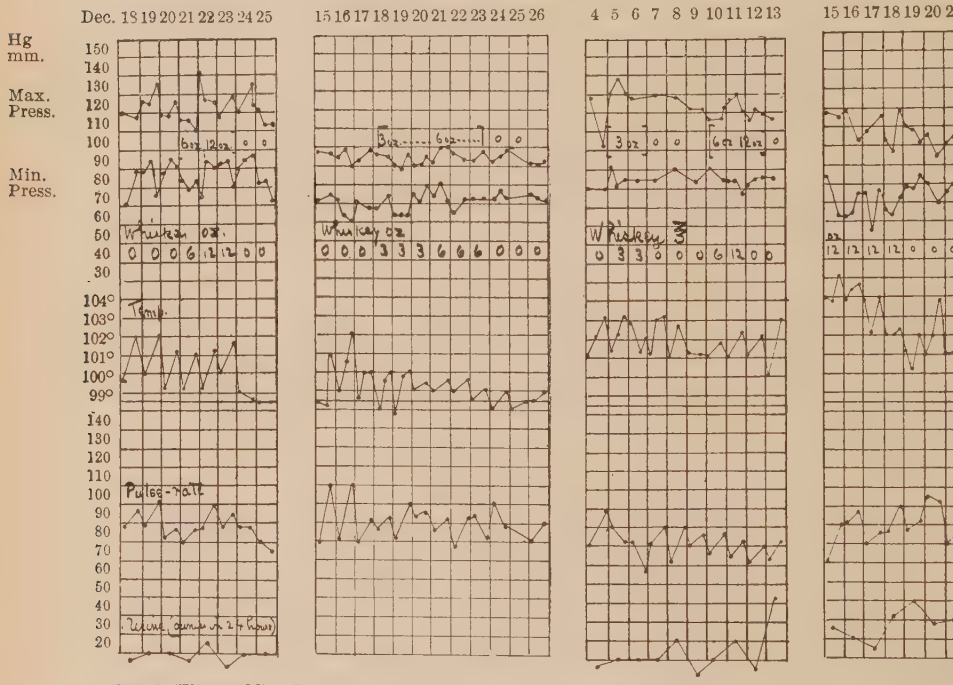
Latinen found a decrease in the number of leukocytes in cases of pneumonia during alcoholic medication, and Massart and Bordet observed a negative chemotactic effect upon leukocytes, even with very dilute solutions of alcohol.

[1] Paris Thesis, 1880.

That it increases in animals the susceptibility to infection and diminishes the animal's power of resistance has been shown so many times and in so many ways that it is not necessary to go over the evidence in detail.

In man something more or less akin to experimental evidence in this matter is furnished by the well-established fact that alcoholics are predisposed to infectious diseases and have them in a very virulent form.

CHART 4. Typhoid.


Dec. 18 19 20 21 22 23 24 25
15 16 17 18 19 20 21 22 23 24 25 26
4 5 6 7 8 9 10 11 12 13
15 16 17 18 19 20 2
Hg mm.
Max. Press.
Min. Press.
Whiskey oz.
Temp.
Pulse-rate
Case 1 (Fitzgerald).
Case 2 (Scroy, aged 6, wgt, 50 lbs.).
Case 3 (Fleming).
Case 4 (Loughl

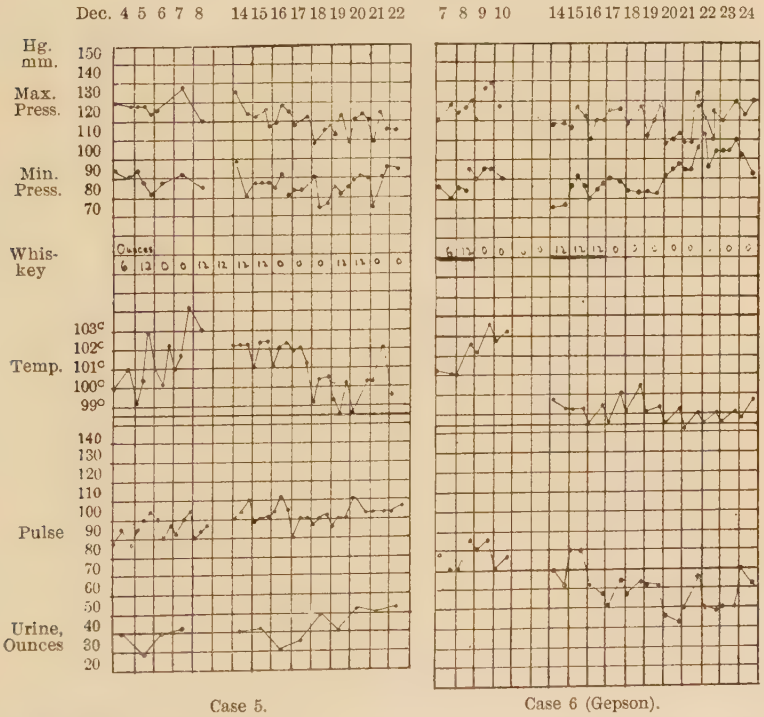
More direct and important evidence is furnished by researches designed to investigate the antitoxic power of the blood in health and in disease with and without alcohol.

Mircoli[1] compared the antitoxic power of normal human blood with that of alcoholics by testing the power of each to neutralize Maragliano's tuberculin. The blood of normal men was found to neutral-

[1] La clinica medica Italiana, March, 1900, p. 133.

ize large doses of this toxin. For example: 10 c.c. of this tuberculin is a fatal dose for animals of one kilo weight; but this animal can be protected against this dose by the injection of 2 to 3 c.c. of normal human serum. The serum of chronic invalids, on the other hand, does not possess this power. But the serum of drunkards was found to be much more strongly antitoxic than that of normal men. In one case 0.1 of a c.c. of drunkard's serum was sufficient to protect a kilo animal against 10 c.c. of tuberculin.

CHART 5. Typhoid.


Dec. 4 5 6 7 8 14 15 16 17 18 19 20 21 22 7 8 9 10 14 15 16 17 18 19 20 21 22 23 24
Hg. mm.
Max. Press.
Min. Press.
Whiskey
Ounces
Temp.
Pulse
Urine, Ounces

Case 5. Case 6 (Gepson).

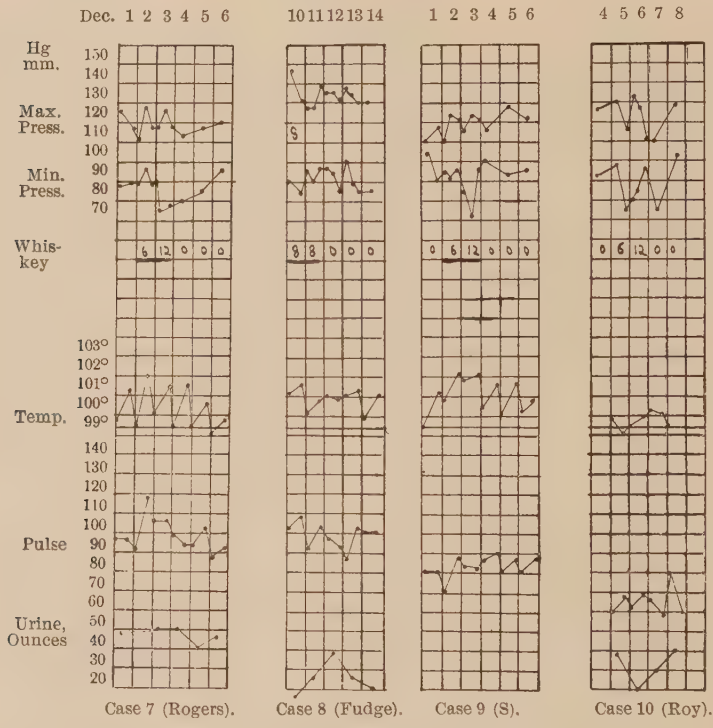
From these facts Mircoli concludes that alcohol is a most valuable remedy for tuberculosis, forgetting that tuberculin and tuberculosis are by no means the same, and that alcoholic cirrhosis and tuberculosis of the lungs, or peritoneum, are very frequently associated. Nevertheless, Mircoli's results are of great interest, both in themselves and as an indication of the direction in which future research should be turned.

More recently Abbott and Bergey[1] have undertaken a study of the blood reactions of normal and alcoholized rabbits by Ehrlich's methods. Their conclusions are:

1. The daily administration of alcohol per os to rabbits reduces the amount of hemolytic complement in their blood.

2. The diminished reactivating power of the blood of alcoholized rabbits is not due to the presence of small amounts of alcohol as such in the blood.

CHART 6. Typhoid.



3. Alcohol not only reduces the amount of complement in the rabbit's blood, but may cause at the same time a reduction in the number of free specific receptors in the blood of a rabbit artificially immunized against an alien blood.

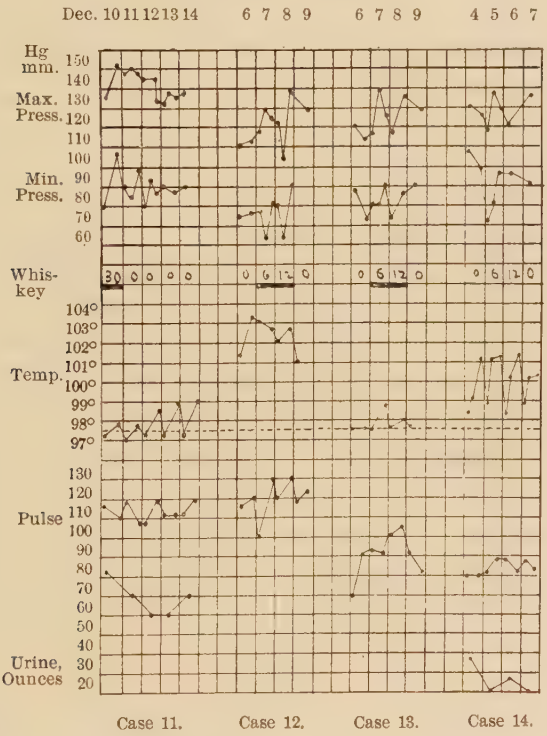
4. The diminished complement, content of the blood of alcoholized rabbits, renders the animal more susceptible to the toxic action of an alien blood.

[1] University of Pennsylvania Medical Bulletin, August, September, 1902.

The Tolerance of Febrile Patients for Alcohol.

It must have forced itself upon the notice of anyone who has watched the effects of alcohol in fever cases that such patients will stand an extraordinary amount of the drug without any signs of intoxication. For example, I recently watched a patient with typhoid in the service of Dr. F. C. Shattuck who took for nearly a fortnight 2 ounces of whiskey every hour, day and night—that is, 3 pints of

CHART 7. Typhoid.



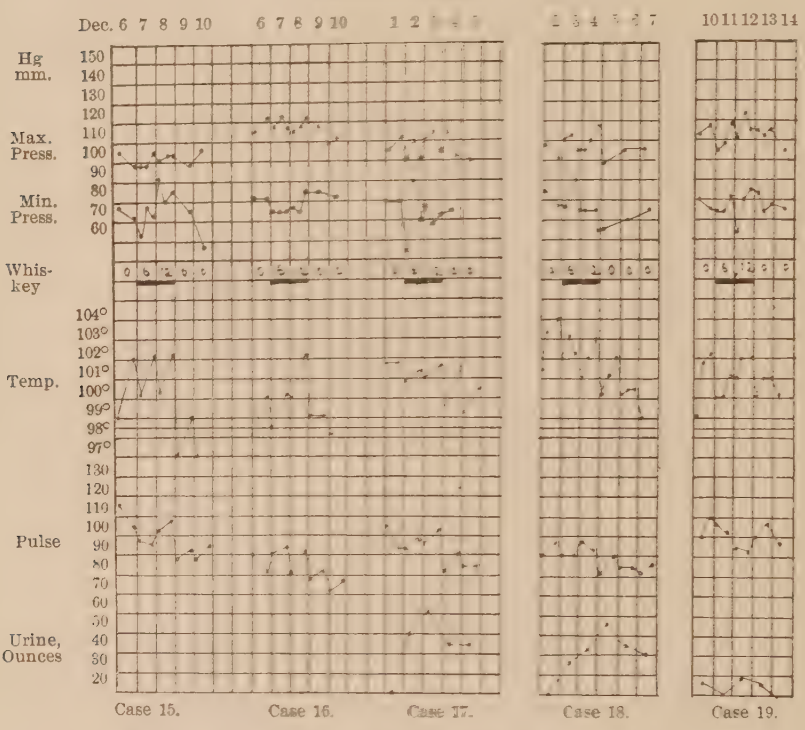
whiskey every twenty-four hours—without any sign of intoxication. In the same service a young girl, also suffering from typhoid, took 60 ounces of champagne—nearly 2 quarts—every day for three weeks without any of the ordinary evidences of intoxication.

This certainly proves that alcohol acts differently in disease and in health, and makes it obvious that the results of experiments with

alcohol on healthy men should not be supposed to prove what its effects in sickness may be.

But because alcohol acts differently in disease, are we obliged to suppose that it acts *more beneficially* than in health?

That we do not smell it in the breath of typhoid-fever patients despite a dosage which would make a well person reek with it does not point to any considerable difference in the amount burned up in



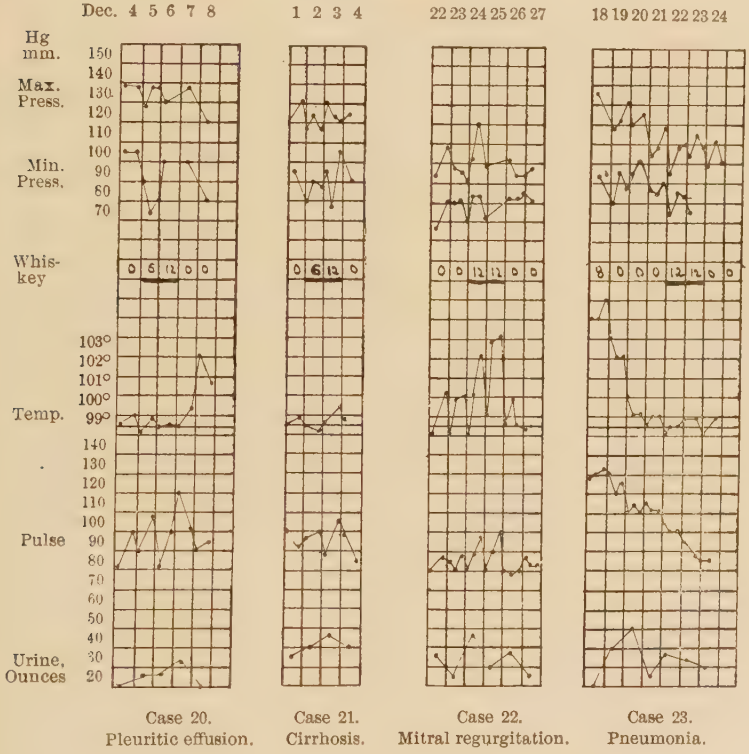
the body, for even in the intoxicated states produced by alcohol in healthy persons 98 per cent. of the alcohol is burned in the body. The alcoholic odor in the breath does not prove that any considerable portion of the alcohol is being excreted through the lungs.

Alcohol given to dogs with sugar does not make them nearly as drunk as when it is given without sugar,[1] but its harmful effects are no less marked.

[1] Rosenfeld. Loc. cit., p. 162.

That sick persons are not intoxicated even by enormous doses of alcohol gives us no evidence whatever that it is doing good, nor, on the other hand, is it a reason for believing that it does harm. It is an interesting but a wholly neutral fact so far as the therapeutic value of alcohol is concerned, and is important chiefly as a warning to those

CHART 9.



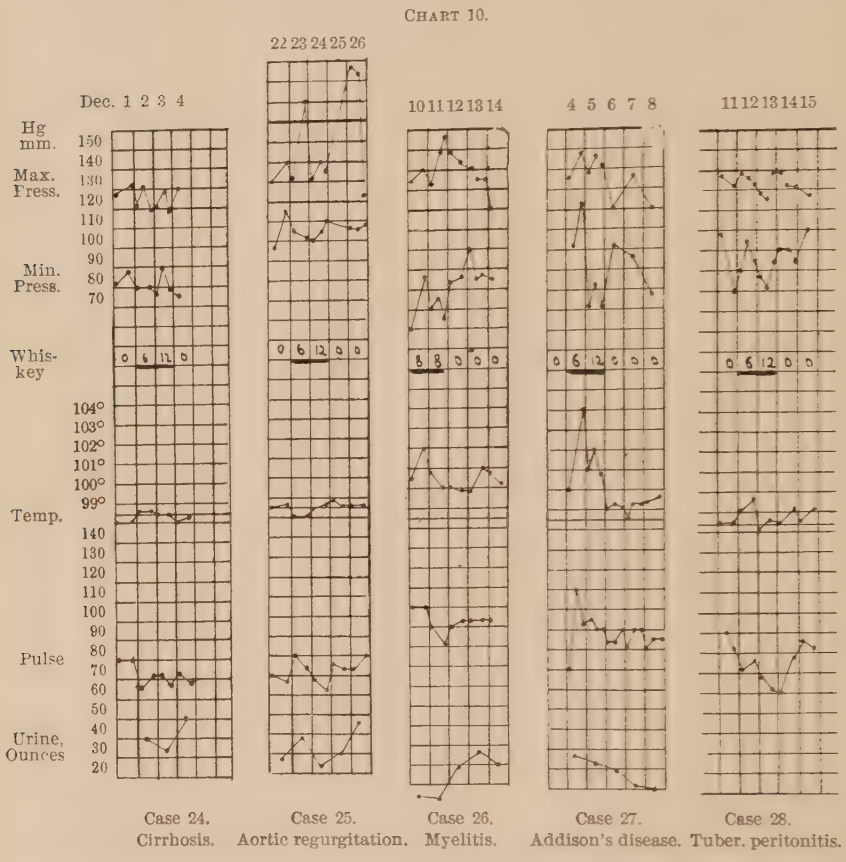
who tend to argue directly from the known effects of the drug in health to its supposed effects in disease.

The Psychic Effects of Giving Alcohol.

1. On the mind of the physician and of the patient's family or friends.

2. On the mind of the patient himself.

1. The virtues of alcohol as a stimulant have been so firmly established in the minds of the laity that both the patient and his friends are apt to be comforted by the knowledge that it is being given. It does not sound exactly like a drug, its taste is generally not disliked, and the cheering impression that something is being done and done



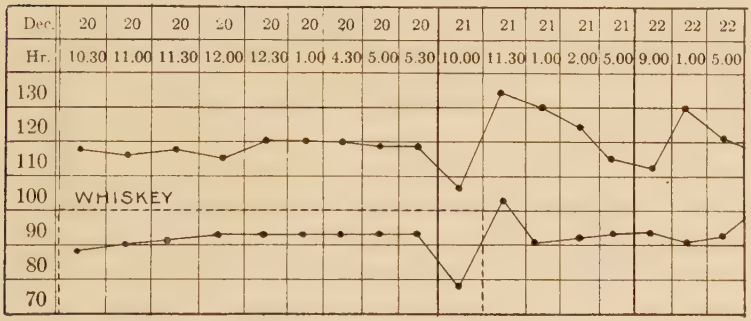
pretty frequently is diffused among those who are caring for the patient, and may reach the mind of the patient himself.

By a sort of autosuggestion a similar impression is sometimes produced upon the physician as well. It is very hard to sit still and do nothing for the patient, and even when we have no very reasonable belief in the efficacy of a drug, it is a relief to the

physician's mind to give *something*, especially something that is welcomed by the patient and his friends, and something of which the community generally has a high opinion. Then the soothing effect upon the patient which the narcotic action of alcohol produces is indirectly soothing to the physician as well, and increases his willingness to prescribe and to continue the so-called "stimulant." In short, alcohol makes physician, patient, and friends more comfortable.

2. The narcotic action of alcohol, its tranquillizing and benumbing effects upon the nervous system, have been very properly insisted on as a therapeutic influence of considerable importance by Cushny and by Meltzer in recent addresses on the use of alcohol in disease. To

CHART 11. Typhoid.



Whiskey, 1 ounce every two hours till here.

The upper line represents systolic pressures, the lower diastolic pressures. Both are measured every half-hour. On the 21st a relapse began; temperature, 102°, pulse, 80 to 90.

save the patient from worrying about himself, from broodings on the cause and apprehensions about the future of his disease, is certainly to do him a service; but we cannot at the same time praise alcohol for bringing the patient into so passive and vegetative a condition, and expect also to take advantage of that active, fighting determination to get well which many physicians suppose to have a real effect in combating disease. Either the tranquillity or the actively resistant will-power of the patient must be sacrificed. Whether either factor has any genuine influence on the course and outcome of disease is entirely a matter of guesswork. We have no definite knowledge in the matter, and all that I mean here to point out is that if we are to

maintain that the narcotic effect of alcohol is beneficial we must give up the idea that the patient's will-power is an important factor in his recovery.

But, although it is generally assumed that alcohol has a benumbing effect and so a tranquillizing effect upon the patient, it has not been my experience that any such effect is always, or even usually, to be observed. That very striking *neutrality* of alcohol which has been my chief lesson throughout all the other observations which I have made on its action has impressed me and surprised me afresh in studying its psychic effect. Only in four out of the sixty-nine cases in which I have watched for the tranquillizing effect of alcohol has any such effect been noticeable. In the vast majority of patients, as I talked with them several times each day during a period of about six weeks, no change whatever in the prevailing mood could be determined. The downhearted patients were not notably more or less downhearted; the cheerful ones were neither more nor less cheerful. One patient especially, in whom the dose of 60 ounces of champagne per twenty-four hours was suddenly cut off, showed not the slightest psychic change that I could detect.

A few of the typhoid patients seemed to sleep a larger part of the day during the time when alcohol was given them; but it was difficult to be sure that this change would not have taken place spontaneously. In one patient, who became more sleepy just after the alcohol was given him, the sleepiness continued just the same for the next ten days after the alcohol was withdrawn; in fact, until the temperature became normal.

Very likely finer psychic tests, such as Kraepelin employed in his studies on typesetters, would have shown that in disease, as in health, the associations and reactions necessary for the more delicate psychomotor processes are slowed by the action of the drug; but that any constant effect was produced on the temper, mood, and spirits of the patient I could not see any reason to believe.

From this résumé it will be seen that no considerable amount of work on the estimation of blood pressure in human beings during the administration of absolute alcohol has so far been done. Rosenfeld's observations are, it seems to me, conclusive so far as concerns the effect of the drug upon dogs, but we cannot immediately reason from its effect in healthy or in tired dogs to its effect in sick men.

Accordingly I have undertaken a series of measurements of the blood pressure before, during, and after the administration of alcohol in patients for the most part sick with typhoid fever in the medical wards of the Massachusetts General Hospital. I am especially indebted for the opportunity to carry out these researches to the kindness of Drs. F. C. Shattuck and R. H. Fitz. Our method of work has been the following:

Two instruments have been used—the Riva-Rocci machine for the estimation of the maximum or systolic pressure, and Oliver's hemodynamometer for the estimation of minimum or diastolic pressure. The working of these instruments may be explained in a few words:

The Riva-Rocci apparatus consists of a dilatable rubber armlet about three inches wide covered with tough canvas as a support to the rubber, and arranged by means of a series of hooks and eyes so that it can be tightly fitted to arms of any size. By means of a V-tube air is blown simultaneously into this armlet and into the bulb of a mercury manometer. For inflation an ordinary cautery bulb was used. The whole apparatus can be constructed for about four dollars, but it is not yet upon the market.

To use the instrument we attach the armlet snugly around the patient's upper arm, about two inches above the bend of the elbow, and force air into it until the radial pulse disappears. When the radial pulse is no longer felt we note the point to which the mercury column has been forced up and record the reading in millimeters. The instrument appears to be very accurate in the sense that different observers, after an equal amount of practice, read practically the same independently, and that successive readings by the same observer in the same patient do not vary more than 3 or 4 millimeters of mercury. It is very easy to use and requires very little practice. It is not at all painful to the patient, as I have ascertained by many experiments upon my own arm; and no patient has complained of it in any way, although in some cases more than a dozen readings were taken in the course of a day. No bad effects upon the arm of the patient have occurred, although the cases selected were mostly typhoid, in which thrombosis is well known to be favored. Any errors that there may be in the instrument may be disregarded in a series of comparative observations upon the same patient by the

same observer, since the errors would be presumably the same in all the measurements.

Oliver's hemodynamometer is a more difficult instrument to use It consists, essentially, of a hollow rubber pad filled with glycerin and water, which is put over the radial artery and through which the pulsations of the artery are transmitted to a rigid rod and thence through a ratchet-and-pinion adjustment to a needle moving upon a clock-face dial. By exerting pressure with the instrument upon the pad the needle is made to revolve, and by suitable pressure the pulse may be obliterated. If, then, we relax the pressure upon the artery until a faint pulsation is permitted, this pulsation begins to be represented by oscillations of the needle. As we relax the pressure gradually more and more the needle upon the face of the dial has a double motion. It moves backward toward the starting point, and it also oscillates back and forth during its course. These oscillations gradually increase up to a maximum as we relax the pressure, after which, if we relax it still more, the oscillations begin to diminish and gradually disappear as the needle approaches the zero of the scale. The maximum oscillations in normal persons occur between the points marked 85 and 110 on the scale, and since the pressure within the fluid pad of the instrument is the same as that within the artery when a point of maximum oscillation is reached, the minimum arterial pressure may be thus recorded. The fluid pad obviates the difficulties of applying the instrument over the uneven surface of the wrist. The soft and elastic surface of the pad adjusts itself among the structures of the wrist and gets into contact with the artery at some point, provided the artery is palpable at all. The chief difficulties in using the instrument are (1) to hold it steady without increasing or decreasing the amount of pressure used upon the artery, and (2) to record accurately the position of the swiftly moving needle. With well-sustained pulses it is very easy to see just where the needle starts and where it ends in each of its excursions, but in the bounding pulses of febrile patients this is often very difficult. With a moderate amount of practice, however, different observers do not vary more than five points in the scale in their readings.[1]

[1] My instrument reads about 25 m.m. Hg too high; consequently I have subtracted 25 from all the records of diastolic pressure in the charts. This leaves the relations between one reading and the next unchanged.

With these two instruments we have made 1169 measurements in fifty-eight individuals. We began by taking observations every half-hour to determine the amount of range of variation at short intervals. Later we took the measurements every hour and every two hours, and, finally, every five hours, as the variations in the smaller periods of time were insignificant, or were excited from moment to moment by occurrences the mark of which would be as likely to escape detection in half-hourly as in four-hourly measurements. Thus a cry or groan from another patient in the ward, the approach of dinner, or the answering of a question needing some thought would send the blood pressure up a number of points, the rise lasting only a few minutes.

We began our four-hourly measurements on febrile patients recumbent in bed and upon unvarying diet. After two or three four-hourly records with each instrument the patient was given either half an ounce of whiskey or an equivalent amount of absolute alcohol, properly diluted and flavored. This dose was repeated every four hours for the first twenty-four hours, and then doubled and continued for twenty-four hours more. After that it was, in the majority of cases, omitted, although in a few it was continued several days more in order to ascertain whether any further effect was produced after the first forty-eight hours. After stopping the alcohol we continued our readings for at least twenty-four hours, and often longer.

Among the cases studied were twenty-five of typhoid fever, two of pneumonia, two of chronic valvular heart disease, two of malignant endocarditis, two of gonorrheal arthritis, and one each of the following: pleuritic effusion, Addison's disease, cirrhosis of the liver, thrombosis of a leg vein, tuberculous peritonitis, myelitis, and phthisis.

Summing up in a few words the total result of these measurements, I may say that they indicate that in cases of the type studied alcohol has no considerable effect either upon the heart's action or upon the tension of the peripheral vessels that can be measured by the instruments employed. I must confess that this result was a great surprise to me. Some effect, either for good or evil, some cardiac stimulation, or some vascular relaxation I had certainly expected to see; but the result, like all those obtained in my investigations of the effects of alcohol on other functions of the body, was practically *nil*.

The following charts and tables give further details of the work:

TEMPERATURE.

	Cases.	Cases.	Cases.
Raised over 0.2; alcohol	149		
" " " whiskey	12—	161	
Lowered over 0.2; alcohol	64		
" " " whiskey	13—	77	
Within 0.2 the same; alcohol	70		
" " " whiskey	1—	71—	309

EFFECTS OF ALCOHOL ON THE TEMPERATURE IN FEBRILE CASES.

Raised over 0.2; alcohol	29		
" " " whiskey	6—	35	
Lowered over 0.2; alcohol	20		
" " " whiskey	8—	28	
Within 0.2 the same; alcohol	4		
" " " whiskey	0—	4—	67

PULSE IN AFEBRILE CASES.

Raised over five beats; alcohol	98		
" " " " whiskey	8—	106	
Lowered over five beats; alcohol	56		
" " " whiskey	7—	63	
Within five beats the same; alcohol	128		
" " " " whiskey	12—	140—	309

RESPIRATION.

Raised over four periods; alcohol	22		
" " " " whiskey	2—	24	
Lowered over four periods; alcohol	27		
" " " " whiskey	3—	30	
Rate the same; alcohol	232		
" " " whiskey	23—	255—	309

FOOD.

Taken the same	212	
Taken better	64	
Takes less well	18—	294

TONGUE.

The same	213	
Better	42	
Worse	20	
Moister and more coated	9—	284

SKIN.

The same	215	
Moister	39	
Drier	12—	266

INSOMNIA.

The same	155	
Better	7	
Worse	8—	170

DELIRIUM.

The same	150	
Worse	3	
Excited and nervous	1	
Better	1—	155
Total number of observations		2163

Summary and Conclusions.

1. In 41 patients, mostly cases of typhoid fever, 1105 measurements of the blood pressure were made before, during, and after the administration of alcohol in therapeutic doses. Neither the maximum nor the mean blood pressure showed any variations that could reasonably be referred to the action of the alcohol. So far as was determined by the methods and in the cases used in this research, the action of alcohol upon the circulation was *nil*.

2. The same neutrality and apparent inertness of therapeutic doses of alcohol in relation to the temperature, pulse rate, respiration rate, appetite, sleep, delirium, and secretions (renal and cutaneous) of 309 patients suffering from a great variety of diseases was the total impression derived from 2163 observations in these cases.

3. These observations are not interpreted as proving that alcohol is useless or useful in disease. As a narcotic and vasodilator it may have an important place in therapeutics, although this is not yet demonstrated.

4. More important, probably, than any of the questions investigated so far is the problem of the effect of alcohol upon the power of the sick man's blood to protect him against infection and other harmful influences. The studies of Abbott and of Mircoli have begun to clear a path in this direction, and we have a certain amount of evidence relative to a similar problem in the lower animals; but as the results of studies regarding the action of alcohol upon animals or upon healthy men cannot be used as evidence of its action in sick men, there is a good field for experimental work in this direction along the lines of Ehrlich's newer methods.

DISCUSSION.

Dr. Welch: I have been very much interested in the communication of Dr. Cabot. In the beginning he may have pointed out the difference between his results and those obtained by experimentation with animals. There has been the greatest diversity in the results of experimenters with animals, but there is one point that all have agreed upon, and that is, that alcohol administered to animals to the point of intoxication increases their susceptibility to infectious disease. They are unanimous in that. Everyone, beginning with Abbott and followed by Natini, and now by a half-dozen

others, all, universally, came to the conclusion that animals to whom alcohol has been administered rapidly become more susceptible to infectious disease; a certain organism given to an alcoholized animal will kill it, while given to the non-alcoholized animal it will survive. There have been only two observations that favor alcohol: one by Gruber, that an animal in a state of collapse after the administration of large doses of a culture of the bacillus prodigiosis was rescued by the administration of alcohol; the other, an experiment by a Frenchman, who demonstrated that the administration of alcohol did not influence their susceptibility.

Another point is as to its influence upon the bacteriolytic power of the blood. Dr. Hare has come to the conclusion that it increases the bacteriolytic power of the blood, and that is a very interesting point. He used the colon bacillus, and that is an organism that is very readily killed by the human blood. The results were obtained in the same individuals, but they were nothing more than one can obtain, and usually does obtain, with normal animals. He found that the colon bacilli increased until within twenty-four hours he got countless colonies with those who had not had alcohol, while with those to whom alcohol had been given in twenty-four hours the bacilli were destroyed. Anyone who has experimented with the colon bacillus knows that this is the case with normal blood, the colon bacillus being killed by perfectly normal human blood. The selection of that particular organism was not a fortunate one, because it is so readily killed.

Then there is, of course, no relationship between the susceptibility to infection and the bacteriolytic power of the blood, as determined in this manner. Some individuals have blood highly bactericidal, and yet are very susceptible to disease. On the other hand, animals whose blood has no bacteriolytic power may be very resistant to disease.

Accepting these results of Dr. Hare, the conclusion would not be justifiable that variations in the susceptibility to disease correspond with the variations in the bacteriolytic power of the blood. I do not think we have any conclusive basis for clinical procedures in the administration of alcohol one way or the other. The experiments on animals are made with much larger doses per body weight than one would think of giving to human beings. The final analysis must come from clinical experience, and we must be very cautious in applying to the treatment of disease the results of these experiments.

Dr. Jacobi: I look upon the results of Dr. Hare's experiments as very conclusive. They teach a great deal about the effects we have observed so long, and are an additional reason why alcohol should be given in a number of infectious diseases in large doses, and, from that point of view, I disagree with the remarks of the last speaker, Dr. Welch. Alcohol has been given in these cases principally as a stimulant, but it is difficult to distinguish in practice between a direct stimulating effect and what I have preferred to call an antiseptic effect. I have always taught that alcohol should be given in large doses in a number of infectious diseases. Dr. Kinnicut will recall a

case of septic diphtheria treated in this manner nearly a generation ago. It was a very bad case and three ounces of whiskey were being given in the twenty-four hours. When the dose was increased to twelve ounces the patient began to improve. These observations of the beneficial effects of large doses of good whiskey in infectious diseases have been made in thousands of cases these forty-five years in which we have seen so much of diphtheria. I recall a case in which a child, aged two years, probably weighing thirty-two or thirty-four pounds, was given a pint of whiskey a day, and after five or six days the child got better. *Then, but then only,* the child showed symptoms of intoxication. In these conditions of sepsis large quantities of alcohol are not felt until the septic condition begins to subside and then the patient is intoxicated. I am delighted with the results of Dr. Hare's experiments and observations. I have known for a long while that unless I gave large doses of alcohol in sepsis my patients die, and that if I do give it they are apt to get well. It is astonishing to observe how much whiskey is tolerated, or rather required, by persons who never touched a drop before, nor will afterward.

Dr. Abbott: I do not feel very hopeful of a correct interpretation of these results. The last research with which I was identified taught me an important lesson. It was found that uniformly the administration of alcohol to rabbits produced a reduction in the amount of hemolytic complement. As our research progressed, however, we found that there was an occasional increase, which was contrary to the general trend of the experiments. We found that wherever there was an increase of the hemolytic factors there was always an inflammatory condition somewhere in the body. This suggested a compensatory action; perhaps an increase of complement incidental to the inflammatory action had masked or counteracted the depressing action of the alcohol. By purposely inducing both septic and aseptic inflammatory reactions we now know, from the investigations of Sweet and of Vedder, that both the bacteriolytic and hemolytic complements may be markedly increased. It is possible that in certain diseased conditions in which alcohol is given we erroneously regard the conditions manifested by the blood as referable to the alcohol, whereas, in fact, they may represent a reaction coincident with the pathological condition and in no way connected with the alcohol.

Dr. F. C. Shattuck: Dr. Cabot refers to a hospital patient, a housemaid, to whom I gave sixty ounces of champagne a day. There is a special reason for the choice of this expensive form of alcohol in her case, upon which I need not dwell. She had a very severe typhoid fever, complicated by double otitis media and coextensive and deep bed-sores. I believe it to have been of great service to her. It seems to me that we are not yet in a position to explain fully what alcohol does in disease. It seems to be burned up and thus to feed the tissues. It *may* be germicidal or antiseptic under certain conditions. We do not *know*. But it seems to me that the clinical evidence in

favor of its usefulness in severe septic conditions is so strong as to cast the burden of proof on those who deny its usefulness. We cannot be blind to the fact that in some diseased states an amount of alcohol is taken without the least sign of toxicity, which, in health, would profoundly intoxicate, and with *apparent* benefit. I welcome investigation of this important subject. The more we know the better for us and for our patients. My reason for speaking is only to state my conviction that alcohol should not be discarded until far stronger proof of its invariable harmfulness is brought forward than has been presented up to this period.

Dr. Musser: The last words of Dr. Shattuck as to the use of alcohol are correct, but I do not think that its routine use in typhoid fever is justifiable. In a series of 80 cases that I have had recently, and the worst I have ever seen, no death occurred, and yet I gave less alcohol than I have ever given in any similar series.

I do not hesitate to give alcohol when I find occurring in the course of typhoid a septicemia, especially where it comes on in old subjects. There we should give it almost *ad libitum*. But the routine use of alcohol in infections is not at all justifiable. In the septic processes we are, of course, well justified in its use in the manner Dr. Shattuck has spoken of.

Dr. Dock: Since the evidence of single cases showing the beneficial action of alcohol has been brought forward, I would like to mention the fact that often the most desperate cases of sepsis pull through without the use of alcohol. As a matter of experiment I have not given alcohol at all for a good many years, and although I have the observation on a good many cases, I do not feel that they furnish information not already known. My typhoid patients, pneumonia patients, and septic patients never get it. Occasionally a patient may get it in convalescence, for reasons other than medical, but only in that way. I could mention many cases of typhoid, sepsis, and other diseases in which no alcohol was employed, and, to the surprise of those believing it essential, the patients recovered.

As an example of the opinion held by some, at one time, when discussing this matter in a medical society, a doctor of great experience stated seriously that everything depended upon using the right brand of whiskey.

Dr. Cabot: Just a word as to this discussion. It seems to be brought out that those who advocate the use of alcohol do so on the ground that it produces some change in the blood—in the protective powers of the blood. The number of those who think this way is certainly increasing, and many of those who now advocate its use do so on the principle that Dr. Jacobi and Dr. Hare have spoken of. If this is true, then it should be used in a routine way and not in selected cases. If it increases the protective power of the blood it should be given in large doses in every case, as Dr. Jacobi has said. We say it increases the bacteriolytic and protective power of the blood and yet give it only in selected cases; but anybody deserves protection if we can give it to him.

ACTINOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM, WITH THE REPORT OF A CASE DUE TO AN UNIDENTIFIED MEMBER OF THE ACTINOMYCES GROUP.

By WILLIAM TRAVIS HOWARD, Jr., M.D.,
OF CLEVELAND, OHIO.

(From the Pathologic Laboratory of the Lakeside Hospital, Cleveland.)

The observation of an apparently primary abcess of the brain caused by a branching, intertwining, thread-like organism similar to those recently found in a variety of lesions, and commonly called streptothrix, but properly classed under the genus actinomyces, led to a review of the literature of actinomycosis of the central nervous system.

Including mine, eighteen cases were found, and of these the nervous system was apparently affected primarily in five and secondarily in thirteen. On comparison many of these are very similar to each other and to my own.

It is my intention in the present article to state the salient features of the cases in the literature, report my own case, call attention to the identity of so-called streptothrix with actinomyces, and, finally, summarize our knowledge on the subject.

I. PRIMARY ACTINOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM.

The first recorded is that of O. Bollinger[1] (1887), who reported the case of a woman, aged twenty-six years, whose illness began, about one year before death, with headache, soon after which there was paralysis of the left nervus abducens. Six months later there was paralysis, with eczema, of the forearms, and about this time she gave birth to a vigorous boy. Headache persisted, and nineteen days before death there was double vision and changes were made out in the left

retina. Death occurred in coma after convulsions. Diagnosis, brain tumor. The lateral ventricles were enormously dilated, and the foramen of Monro and the third ventricle were distended by a growth the size of a hazelnut, with smooth surfaces, and of a bluish-gray color. On section a mucoid, sticky fluid escaped. Microscopically the mass was composed of granulation tissue containing numerous typical colonies of actinomyces. No other focus of actinomycosis was to be found in the body. The woman is said to have had bad teeth.

Almquist[2] (1890) reported the case of an artilleryman who died after a two weeks' illness with cerebrospinal meningitis. The autopsy was made twenty hours after death. Plate cultures made from the base of the brain and from the lateral ventricles gave colonies of a large micrococcus, bacillus proteus, and a single colony of a streptothrix. This organism grew well on gelatin, forming rather large, convex, hemispheric colonies and causing liquefaction of the medium. On agar there was a rapid, luxuriant growth, with larger and smaller white crusts. In both there was a flaky growth, with a thin surface crust. Microscopically there was a mycelium of unjoined threads with true and frequent branching. The threads averaged 0.5μ in diameter and sometimes reached 100μ in length. Air hyphæ which broke up into small cubical or oval cells appeared on the white crusts. Both cells and threads stained lightly with the anilin dyes. No mention is made of finding this organism in the pus or sections of the meninges, or of animal experiments. Absence of microscopic proof of the presence of this organism in the lesions and the fact that a single colony was obtained in the cultures lend strong probability to the natural inference of air contamination. I am, therefore, very strongly inclined to question the propriety of including this case.

In 1895 Ferré et Foquet[3] reported the case of abscess of the brain of a man who during life had epileptiform crises. From the description the brain abscess was probably primary. From the pus they obtained a "streptothrix" in pure culture. The organism grew well on the various media, but best on potato. Microscopically it was made up of ramifying filaments with knob-like terminations. The organism stained by Gram and was not pathogenic for guinea-pigs. On subdural inoculation of a rabbit there was general diffusion of the parasite in the organs without reaction or the formation of pseudo-tubercles.

Musser, Pearce, and Gwyn[1] in 1901 reported a case of probably primary brain abscess in a man twenty-four years old. "At a point just posterior to the upper portion of the fissure of Rolando is an area 3 cm. in diameter which is fluctuant, grayish-yellow in color." The side of the brain affected is not mentioned. On section at this point there was found an abscess 2.5 cm. in diameter, containing thick, partly chocolate-colored and partly grayish-yellow fluid of the consistency of oil. No granules were made out. The walls of the cavity were greenish-gray in color and soft and necrotic. The brain tissue about the abscess was softened and of a yellow color. The pus had a foul odor. (The striking resemblance to the abscess in my case will be noted.) The rest of the brain was normal. The ears and the bones of the skull appeared normal. The other organs could not be examined. In the pus of the brain abscess after search there was found a large, ball-like, tangled mass, made up of long, irregularly staining filaments. There was some suggestion of branching of the periphery of the mass. Histologic examination of the abscess wall showed a large mass of radiating threads, which at the periphery were long and thin and stained irregularly. The whole had the appearance of an actinomyces colony. Clubs and rosettes could not be demonstrated. No tubercle bacilli could be found. Aerobic and anaerobic cultures and animal inoculations (guinea-pigs) were negative.

J. C., male, white, aged fifty-two years, was admitted to the medical wards, service of Dr. Edward F. Cushing, of the Lakeside Hospital, April 21, 1902. The patient had been an orderly in the hospital for a number of years and always been well until his present illness. Several days before his illness he had complained of not feeling well, and for two days before admission to the ward he had not reported for work. On the morning of April 21st he was found in his room in a condition of stupor. He was very drowsy, but on being aroused could answer questions and complained of pain in his right eye. The conjunctiva of this eye was reddened; the other pupil was markedly dilated. The left eye and pupil appeared normal. The patient could move his hands and arms and there was no evidence of paralysis. His eyes were examined by Dr. Millikin, who found nothing abnormal. Physical examination disclosed nothing further except varicosity of the veins of the left leg. Ulceration of the leg is not mentioned in the clinical history and was therefore probably not present. On April 22d his condition was much the same, but questions were answered with difficulty and stupidly. The right pupil was dilated and did not react to light. Breathing was regular and somewhat accelerated. The pulse was full sixty-four to the minute. Physical exam-

ination of the thorax and abdomen was negative. The knee-jerks on both sides were much increased. On the left side there was a marked Babinski reflex. The patient could move his upper and lower extremities, but there was marked rigidity of the muscles of the left arm and to a less degree those of the left leg. The temperature ranged between 100° to 101.5° F. There was involuntary micturition and defecation. On April 23d the note made records that the patient continued throughout the preceding day in a comatose state, and during the night the coma deepened. At times he was quite restless and complained of pain in the right side of the head. To-day there was deep coma from which he could not be aroused. The right pupil was still widely dilated; the reflexes were the same as yesterday. There was now rigidity of the right arm and leg, with paralysis of the left arm and leg. Breathing was stertorous, but not especially rapid. The pulse was strong and eighty to the minute. The leukocyte count showed twelve hundred per cubic millimeter. There was no discharge from the ears, the membranes appeared normal. He was transferred to the surgical service of Dr. Dudley P. Allen, who trephined over the motor area of the right side. There was distinct bulging of the brain when the dura was cut through. The meningeal vessels were markedly congested, but no hemorrhage and meningitis and no evidence of brain abscess were found. The rigidity of the arms became less marked after incision of the dura. The patient died at 5.40 the afternoon of April 23d. Autopsy six hours after death. The body was fairly well built and nourished and 170 cm. in length. Rigor mortis was present. The right side of the head was shaved, and over the right parietal region there was a semicircular wound closed with sutures. The right pupil was somewhat larger than the left, which was of ordinary size. The external surface of the left leg was the seat of a large varicose ulcer. Near this there were a number of scars of former ulcers. No other scars were to be seen. The head was of ordinary size and shape. The wound above referred to was healthy in appearance and free from pus. The skull was of ordinary thickness and appearance. There was no softening. The dura at and near the seat of the operation was markedly congested. The brain and piaarachnoid bulged slightly at the opening. The piaarachnoid over a considerable area was congested and in a large vein just beneath the wound contained a dark red thrombus. On removal of the brain, the superior temporosphenoidal and the superior marginal convolutions of the right side were somewhat softer than usual. About the middle of the superior temporosphenoidal convolution and 15 mm. below the trephine hole through the skull there was an area of fluctuation just beneath the surface. On handling the brain it ruptured at this point with the escape of a considerable amount of dark, grayish-green, thick pus, with a foul, putrid odor like that of butyric acid fermentation. On incision in this region there was an abscess the size of a walnut, surrounded by several smaller abscesses varying from 3 to 15 or 20 mm. in diameter. They all had soft, necrotic walls, and were evidently recent. The brain tissue for some distance, 4 cm. in some places, on all sides of the main abscess was soft, edema-

tous, and of a peculiar, gelatinous consistence and appearance. The abscesses with the area of softening extended anteroposteriorly from the ascending frontal to the angular convolution and internally nearly to the right lateral ventricle. The piaarachnoid over the abscess was markedly congested and cloudy in appearance. On section of the brain no other abscesses were to be found. The structures at the base and all the vessels appeared normal. The sinuses were free from thrombi and the middle ears and mastoid cells were normal.

The spinal cord was not removed.

Chest. The muscles were well developed; the costal cartilages were calcified. Both lungs were bound to the chest wall by dense, fibrous adhesions; both pleural cavities were almost completely obliterated. Both lungs were voluminous and on section markedly congested and edematous. No areas of consolidation were to be found. The bronchi contained frothy, blood-stained serum. The bronchial glands were pigmented, but otherwise were normal. The pulmonary vessels were normal. The trachea, tongue, and thyroid were negative. The heart, liver, kidneys, spleen, stomach, intestines, and other organs showed nothing of present interest and their description is therefore omitted.

The thick, creamy, grayish-green appearance and the butyric acid odor of the pus of the brain abscess reminded me at once of pus with similar characteristics obtained some years ago from two cases of empyema from which an organism apparently belonging to the ray fungus group was obtained; so cover-slips were examined immediately during the progress of the autopsy. The pus was rich in polymorphonuclear neutrophilic leukocytes and showed a few scattered bacillus and thread-like forms. In several preparations stained by Gram's method larger and smaller clumps of branching threads were found. A few leukocytes containing bacillus and long, thread-like forms were seen in some preparations. The threads varied very much in length and to some degree in thickness. The bacillus and thread-like forms varied from three to thirty or forty microns in length. As a rule they stained deeply and uniformly with fuchsin and gentian violet in either aqueous or anilin solution, but many, especially the shorter forms, *i. e.*, those of four to eight microns in length, showed larger or smaller unstained areas which usually involved the whole thickness of the organism. In some of these forms with unstained areas a thin cell membrane was discernible. The organisms varied from 0.3μ to 0.5μ in thickness, the former being the average. Some forms showed irregular slight swellings, which were usually situated at one or the other end. No typical knob or club-like forms could, however, be found. The ends were usually square, were often rounded, especially in the shorter forms. Many of the longer forms were wavy in outline. Some of the shorter forms were bent, forming almost comma shapes. Some threads and rods showed transverse division into short bacillus and even coccus forms, and thus chains of bacilli and cocci were not uncommon. The latter forms were always larger than streptococcus pyogenes. The mass

of intertwining branching threads showed no special spore-bearing structures; careful search failed to demonstrate the presence of clubs. The forms were non-septate, and the branching was true, the protoplasm of the main stem always being directly traceable into the branches. In the larger clumps the growth was always radiating, and the mycelium formed a distinct feltwork. No capsules could be made out.

Numerous cultures, both aerobic and anaerobic on slants and on Petri plates, were made on various media, including plain glycerin and glucose agar and potato with glucose bouillon and chest serum, from the pus of the brain abscess. Care was taken to use a large amount of pus for sowing the cultures. In many of the cultures streptococci, which reacted in every way to the tests for streptococcus pyogenes, grew. In none of the cultures were there forms suggestive of those found on the cover-slips. Following the plan of Norris and Larkin, attempts were made to grow the organism on the organs of newly-killed rabbits, but always without success. Aerobic plate cultures from the lungs gave streptococcus pyogenes and staphylococcus pyogenes aureus (a few), from the liver and kidneys streptococcus pyogenes.

A rabbit and a guinea-pig were inoculated at once intraperitoneally.

The guinea-pig remained well and was killed six weeks later and showed no lesions.

The rabbit died twelve days after inoculation, and showed a widespread purulent peritonitis, the peritoneal cavity being distended with a large amount of thick, white, sticky pus of the consistency of thick cream, with a well-marked butyric acid odor. The surfaces of the liver and spleen, as well as those of the intestines, were covered with similar material. Cover-slips showed no branching forms, but numbers of long and short threads, bacillus and coccus forms, with leukocytes. Cultures from the peritoneum showed a few colonies of streptococcus pyogenes, but no other organisms.

Pus from the peritoneal cavity was inoculated into the pleural cavity of a rabbit (rabbit II.), which died in three days with extensive purulent pleuritis and pericarditis, and pus from this inoculated into a third rabbit (rabbit III.) caused its death in two days with identical lesions.

Other rabbits were inoculated intravenously with pus from the peritoneal cavity of rabbit II., died within a few minutes with extensive thrombosis of the right ventricle, and one inoculated into the trachea died during the night with purulent pleuritis (rabbit IV.).

Histologic examination and sections from various portions of the brain showed as follows:

Brain Abscess. A number of sections cut in both celloidin and paraffin and stained in hematoxylin and eosin, toluidin blue and eosin, anilin oil, gentian violet, followed by anilin oil and xylol, Weigert's gentian violet method, anilin oil fuchsin followed or not with iodin, decolorized with anilin oil, and Mallory's stain for clubs; Weigert's stain followed by anilin fuchsin, and the Ziel stain for tubercle bacilli.

The abscess was made up of a thick mass of cells, most of which were

polymorphonuclear neutrophilic leukocytes, among which there were both large and small mononuclear cells. About the margins of the abscess the tissue was infiltrated with the same varieties of cells, and often contained red blood cells. Many of the cells were necrotic; nuclear fragments were numerous. The brain tissue for a considerable distance from the abscess proper was edematous, and contained collections of leukocytes. The blood-vessels were markedly dilated, and in many places there was marked perivascular cellular infiltration, with proliferation of the endothelium of the perivascular lymphatics. No microorganisms were found in the blood or lymph vessels. The only microorganisms to be found were clumps of long threads always lying near the centre of small abscesses or about the margin of a large abscess. These organisms were sometimes seen singly or in small clumps, but nearly always formed larger or smaller colonies from twenty to one hundred microns in diameter. These colonies were composed of branching non-septate threads, which formed a meshwork and radiated from the centre of the colony. These colonies when cut through the centre were nearly round in outline and had often rather regular but somewhat serrated margins. In sections stained with hematoxylin or methylene blue the colonies are finely granular and stain homogeneously with the blue stain. No organisms were made out even at the periphery.

In very thin sections stained with eosin followed by Weigert's fibrin stain, very beautiful pictures were given. Here the colonies appeared composed of a finely granular pink ground, traversed by radiating, intertwining, branching dark blue threads, which projected from the margin of the colony in an irregular, wavy line. The finely granular, structureless, pink-staining mass appeared to support the mycelium of branching threads. The threads were usually more thickly placed at the border of the colonies, and while on first examination the outlines of the colonies were uniform, closer study showed that many threads projected for some distance from the colonies between the surrounding leukocytes. Hence the relation between the colonies and the surrounding leukocytes was an intimate one. No leukocytes were ever, however, found penetrating the colonies, although they approached individual threads. These projecting threads never formed clubs, and showed no special tendency to break up into short bacillus and coccus forms. Near the colonies both long and short free threads were to be found. Reverting to the threads in the colonies, they stained well with anilin gentian violet and both anilin and carbol fuchsin, and retained the stain tenaciously whether treated or not with Lugol's solution or exposed to anilin oil or alcohol.

The threads were of about the same size as those described on cover-slips made from the fresh pus. They often showed unstained spaces and irregular lateral swellings or bulging of the cell membrane. Many were wavy and tortuous in outline. The threads took the stain very differently—some deeply and others very faintly. No clubs were found. The threads were not septate. No spore-containing bodies were seen. Here and there among the leukocytes were larger and smaller masses of threads, some of which were evidently parts

of colonies, while others represented detached masses. The threads readily yielded the fuchsin and gentian violet stains on treatment with acids in either weak aqueous or alcoholic solution, and therefore do not belong to the acid fast fungi.

Sections, including the piaarachnoid, over the abscess and near the seat of operation, showed congestion of the bloodvessels and leukocytic infiltration. No threads were found here. Histologic examination of the other organs showed no acute or chronic lesions in any way suggestive of reaction to this fungus.

Animal Experiments. Sections of the peritoneum over the abdominal wall, liver, and intestines of rabbit I. showed swelling, desquamation, and necrosis of the endothelium in places, with an exudate of leukocytes. The leukocytic accumulation varied markedly in extent in different places. There was a notable absence of fibrin. Most of the leukocytes were of the polymorphonuclear neutrophilic type. Among the leukocytes there were in many places great numbers of bacillus and streptococcus forms. In some places long threads were seen, but no branching forms could be found. The threads were never in the form of colonies, as in the brain abscess, but were met with singly or in scattered clumps. They were of the same size, general appearance, and had the same staining characters as those described in the brain abscess. The same applies for the bacillus and coccus forms. Many of the former were curved or bent, and the latter were on the whole larger than streptococcus pyogenes. No nodular formations were present in the peritoneum or in the organs. Sections of the lungs and pleura and pericardium of rabbits II. and III. showed widespread purulent exudation, without recognizable fibrin or the formation of definite nodules. The microorganisms were even more numerous in these exudations than that of rabbit I. They had the same characters, with the exception that here clumps of definite branching forms could be found. There were no well-marked colonies, but somewhat elongated masses of interlacing threads, some of which showed true branching. The shorter, non-branching bacillus and coccus forms were, however, much more numerous. In both animals, as in the brain abscess, there was a certain amount of phagocytosis on the part of the polymorphonuclear leukocytes, some of which contained numbers of short threads or forms.

The parenchyma of the lungs of rabbit II. was not appreciably affected, and no organisms were found in other organs. The organisms had the same staining reaction noted for those in the brain abscess.*

Including Almquist's rather doubtful case, there are five known cases of primary cerebral actinomycosis, three of which have been reported as instances of "streptothrix" infections. In all except

* My thanks are due to Drs. Cushing and Allen for the use of the clinical history of the case.

Bollinger's case, the only one to show the changes of "typical actinomycosis," the course of the disease was acute. In this case the diagnosis was brain tumor. In one case the diagnosis was tuberculous meningitis, in another cerebrospinal meningitis, and in one cerebral hemorrhage. Four cases were males and one female; all were adults.

The organisms were cultivated in two cases (Almquist and Ferré et Fouquet), and not classified as typical actinomyces, but as "streptothrices."

Pathogenesis for animals was tried in four cases, and was positive in only one (mine).

II. SECONDARY ACTINOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM.

The earliest reported case of secondary cerebral actinomycosis is that of Ponfick,[5] described in his work on actinomycosis in 1882, and quoted by O. Bollinger. A woman who had actinomycosis of the neck and prevertebral tissue developed actinomycotic masses of the left cerebral hemisphere, as well as of the pericardium, lungs, and spleen. In a second of Ponfick's cases an actinomycotic process extended directly through the skull and invaded the pia and the right temporal and frontal lobes.

Kohler,[6] in 1884, reported the case of a man with a number of fluctuating nodules on the surface of the body which were mistaken for glanders. At autopsy there were found ulceration of the upper jaw and sternum, and abscesses of the brain, neck, tongue, spleen, liver, kidneys, and colon. In the tenacious green pus of the various abscesses there were small, greenish masses, which on microscopic examination proved to be colonies of a ray fungus. No mention is made of cultures or animal inoculations.

O. Israel,[7] in 1884, described the case of a laborer, aged thirty-one years, who entered the hospital with a number of ulcers and abscesses on the surface of the body. At autopsy there were found ulcers of the skin of the chest, pericardial adhesions, abscesses of the heart, spleen, liver, kidney, intestine, and brain. Numbers of actinomyces were found in the pus from the skin lesions.

Naunyn,[8] in 1888, reported the case of a girl, aged sixteen years, who died with the symptoms of chorea. At autopsy there were small excrescences on the mitral valve and reddish-brown masses on the

cerebral pia mater. In both lesions a branching, thread-like organism was found. Cultures and animal experiments were not mentioned and were probably not made. It is interesting to recall that Zopf, to whom specimens were submitted, classified the organism as a species between cladothrix and leptothrix.

Keller,[9] in 1890, reported the case of a female, aged forty years, who had pleurisy in 1885, and who in 1886 developed an abscess over the sixth and seventh costal cartilages. Actinomyces were found in the pus of these abscesses. Two years later she was taken ill with convulsions, paralysis of the left side, and coma. At operation, and later at autopsy, chronic meningitis and a small abscess at the right side of the brain were found.

In 1891 Eppinger[10] described, under the title "*Ueber eine neue pathogene Cladothrix und eine durch sie hervorgerufene Pseudotuberculosis (Cladothrichica)*," a case of brain abscess and meningitis associated with changes in the bronchial and supraclavicular glands. The patient was a glassworker, aged fifty-two years, who developed what was apparently joint rheumatism. Eight days later he was unable to work. Later there was paralysis of the left side, tenderness of the right side of the head, delirium, and coma. Death occurred after an illness of twelve days. At the autopsy the skull was healthy. There was well-marked cortical, basal, and spinal meningitis, the exudate at the base of the brain being thick and sticky and of a yellow color. The brain tissue was congested and soft; the lateral ventricles were distended with yellowish pus. Communicating with the right lateral ventricle through an opening in the optic thalamus there was a large abscess of the right hemisphere extending from the middle of the frontal to the occipital lobe. The abscess was filled with pasty pus; its wall was thick and rather firm. There were firm nodules in the lungs and pleura (pseudotuberculosis). The bronchial and mediastinal lymph glands contained firm, grayish-white nodules. The right supraclavicular glands were very much enlarged and soft.

In cover-slips, and in cultures from the brain abscess, the meningeal exudate, and the bronchial and supraclavicular lymph glands, Eppinger obtained a branching, thread-like organism growing in star-shaped colonies which produced pseudotuberculosis in both guinea-pigs and in rabbits. This organism, which grew readily on ordinary culture media, has been classed by Kruse, Lehmann and

Neumann and others as streptothrix eppingeri. MacCullum, who has recently isolated the same organism from a case of peritonitis, correctly classes it under the actinomyces, as actinomyces asteroides.

Sabrazés et Rivière[11] (1894) described the case of a man, aged thirty-one years, an alcoholic, who was said to have been ill for three weeks before admission to the hospital. Ten days before admission he showed marked mental disturbance. The day of his admission he was aphasic, had great pain in the head, vomiting, and obstinate constipation. He soon became comatose and died.

Diagnosis, tuberculous meningitis.

At the autopsy the meninges were found normal. The left cerebral hemisphere was markedly edematous, soft, and almost difficult. There was an abscess the size of a small orange in front of the centrum ovale in the prefrontal region and involving the first and second frontal convolutions. The apices of both lungs were consolidated and one contained a small abscess. The right kidney was the seat of a large infarct. In the green pus of the cerebral abscess there were long, branching filaments, some showing unstained areas. Chains of irregular, micrococcus-like forms were also seen. The same appearances were met in the renal infarct, where coccus and rod forms as well as masses or colonies of interlacing filaments were also plentiful. The colonies were circular in shape and had a radiated appearance. The ends of the filaments were regular, and showed neither swelling nor diminution in size. Sections of the brain abscess showed edema and disintegration of the brain tissue, with inflammation; but no organisms were found. Sections of the renal infarct showed them, however. No filaments were found in the lesions of the lungs. The organism failed to grow aerobically, but an anaerobic gelatin culture gave, after five days, a single colony of branching, filamentous organism like that found in the brain and kidney. Transplantation was unsuccessful. A guinea-pig inoculated with the pus from the brain died in two days of septicemia due to a micrococcus.

As no organisms were found in the pulmonary lesions, the portal of entry is obscure and the primary seat of the affection is uncertain. It is probable, however, that more careful investigation would have discovered the fungus in the lungs. The bronchial glands were not mentioned.

The authors regard their organisms and that of Eppinger as different from that of actinomycosis.

Dolore,[12] in 1896, recorded the case of cervical and facial actinomycosis with loss of consciousness, delirium, convulsions, and opisthotonos. At autopsy there was found marked cerebrospinal pachymeningitis, in the exudate of which there were yellow granules, which on microscopic examination proved to be actinomyces.

In the same year C. F. Martin[13] reported from Chiari's laboratory two cases of secondary actinomycotic abscesses of the brain. In the first, a man, aged thirty-eight years, with actinomycosis of the lungs, sternum, and ribs, there was a metastatic abscess of the left occipital lobe. Actinomyces were found in the pulmonary lesions, and in the pus of the cerebral abscess. In the second, a boy of sixteen years, there was actinomycosis of the right lung and chest wall, with metastatic abscesses of the right cerebral hemisphere, the right lung, and the kidneys. The secondary abscesses were acute and contained numbers of actinomyces, clubbed forms being rare. Yellow granules were visible in the pus of both the skin and the cerebral abscesses. No mention is made of cultures or animal experiments.

In 1900 Chiari,[14] under the title of "*Ueber Myelitis suppurativa bei Bronchietasie*," recorded two cases of meningitis and abscesses of the central nervous system containing branching threads which he regards as identical with, or closely related to, actinomycosis. Both occurred in males with bronchiectasis. Sections of the bronchiectatic cavities which were made in one of these cases showed the same organisms found in the lesions of the nervous system ; hence Chiari regards the latter as secondary in both cases.

In the first, a man, aged forty-three years, there was a large abscess of the cerebellum, multiple abscesses of the cord, with cerebrospinal meningitis. In addition to pneumococcus, bundles of branching threads without peripheral clubs were found in these lesions. There was no growth in cultures after two days, and no animal inoculations were made. The masses of threads were thin, showed true branching, and took the various stains, including Gram's. Club formation was not observed. Chiari states that the organism of this case had the same microscopic appearances as those found in Martin's above-described cases of secondary cerebral actinomycosis, in which the

"drusen" of the cerebral abscesses lacked peripheral clubs, though the latter were present in the lesions in the other organs.

Chiari's second case was a man, aged thirty-seven years, who had chronic purulent bronchitis, with saccular bronchiectasis of the right lower lobe, purulent cerebrospinal meningitis, with an abscess of the left frontal lobe. The brain abscess and sections of the wall of the bronchiectatic cavities showed numerous bundles of branching threads similar to those found in the first case, with the exception that some threads showed peripheral clubs.

No cultures or animal inoculations were made.

III. CLASSIFICATION.

It is quite evident that the microorganism found in my case does not belong to the lower bacteria on the one hand, and lacks some of the characters usually regarded as distinctive of the typical actinomyces on the other. We have to deal with an organism which forms a mycelium of elongated branching, intertwining, or interwoven threads, which break into beaded segments forming chains of coccus and rod-like forms, but which apparently does not form clubs or club-shaped hyphæ. It caused in rabbits diffuse suppuration in the subcutaneous tissues and diffuse peritonitis without nodules and without typical mycelia, only long and short threads which sometimes branched; coccus and bacillus forms being present in the exudates. Failure of the organism to grow in artificial media and on the organs of freshly-killed rabbits interferes seriously with its comparison with somewhat similar organisms described as actinomyces, streptothrices, and pseudoactinomyces. The terms "cladothrix" and "leptothrix" clearly do not apply here, and the term "streptothrix," though used by Eppinger,[10] Ferré et Foquet,[3] Sabrazés et Rivière,[11] Flexner,[15] Norris and Larkin,[16] Musser, Pearce, and Gwyn,[4] and others for organisms more or less closely corresponding to mine is a misnomer, as Lachner-Sandoval[17] and Hektoen[18] have clearly pointed out.

Kruse[19] and Lubarsch[20] are largely responsible for the application of the term "streptothrix" to the group. Lubarsch would include under the group name of streptothrix, placed midway between hyphomycetes and schizomycetes, all ray fungi, as well as those organisms usually classed as bacteria, which occasionally produce true branches

in cultures and ray forms in the animal organism, regarding the various members of the group as transition stages. As a distinct family of the streptothrix group, Lubarsch would separate those organisms which occur in ray form in the tissues, calling them ray fungi.

Hektoen[18] strenuously objects to the bringing together in a closed circle the most typical member of the group, actinomyces albus, with the most atypical or imperfect, as the tuberculomyces, for instance, simply on the strength of what many in opposition to Lubarsch and others regard as a pathologic condition—namely, club formation.

Hektoen further points out the illogic and untenable position of those who use in this connection the term "streptothrix," a term used by Corda in 1839 for an entirely different family of hypomycetes. Hektoen, therefore, following the lead of Gasperini, Berestenew, and Lachner-Sandoval, insists, according to the principle of priority, upon the use of the term "actinomyces" for this group. MacCallum[21] and Abbott and Gildersleeve[22] have recently emphasized this.

Lachner-Sandoval[20] recognizes twenty-nine species of ray fungi, and as some of these forms have not been cultivated on artificial media the group may be smaller, owing to unknown duplicates. Many new species must be added if the term is to include all the branching, mycelium, and club-forming organisms now classed as bacteria (the acid-resisting bacilli, bacillus diphtheria, etc., see Abbott and Gildersleeve[22]).

Berestenew[23] concludes that the ray fungus disease, caused by parasites of genus actinomyces, to which various names, such as streptothrix, oospora, nocardia, etc., have been given, may be divided into (*a*) typical actinomycosis (such as described by Bollinger and J. Israel, Wolff, Boström, and others); (*b*) atypical actinomycosis without granules in the pus and without spherical masses of the parasites in the tissues, to which belong the cases of v. Eppinger, Sabrazés et Rivière, as well as certain cases of Berestenew and others; (*c*) pseudoactinomycosis, that is, cases with all the symptoms of typical actinomycosis, and caused by different micro-organisms: (1) those which stain by Gram and which, like bacillus tuberculosis, possess the property of forming branched threads with clubs, and (2) those caused by bacteria which do not stain by Gram's method. He describes several cases of pseudoactinomycosis.

Silberschmidt,[24] writing in 1901, studied the organisms from seven cases of human and two of bovine actinomycosis. Of the human cases, one was unusual as involving the lungs, liver, and thigh, three were cases of infection of the lower lacrymal duct, and three were typical clinical cases of actinomycosis (jaw, mouth, and back). With the exception of two of the forms from the lacrymal duct, all showed great similarity in their cultural characters, but none corresponded morphologically with the form described by Boström as the only cause of human and bovine actinomycosis. There was great similarity to the forms described by Wolff and Israel, but there were many cultural differences.

Silberschmidt regards as similar to his the organisms from two of Berestenew's cases of so-called pseudoactinomycosis.

He quotes Poncet and Berard's description of the points of difference between actinomycosis and pseudoactinomycosis:

1. In actinomycosis the mycelium consists of hair-like, radiating threads with numerous peripheral clubs, while in pseudoactinomycosis the mycelium is more interlaced or interwoven and not radially arranged, the branching less frequent, and the spores "lightly stained," the organism having more the appearance of leptothrix.

2. The actinomycosis fungus is more difficult to cultivate and may be either aerobic or anaerobic, while in pseudoactinomycosis the growth is more luxuriant and microscopically made up mostly of forms like bacillus diphtheriæ, but with neither granules nor long threads.

After comparing the cultures from his own cases with each other and with others obtained from l'Institut Pasteur and Kärl's laboratory, Silberschmidt makes the following groups:

1. Growth aerobic and at room temperature; colonies on agar and blood serum are adherent to and send out numerous mycelial outgrowths into the media.

(*a*) Liquefies gelatin; threads long, interlaced, and unbroken; includes actinomycosis hominis and bovis (Boström and others), and actinomyces maduræ.

(*b*) Does not liquefy gelatin; threads broken and often appearing in short forms actinomyces asteroides (Eppinger), actinomyces Capræ (Silberschmidt).

2. Colonies not adherent to media; no offshoots; gelatin not liquefied,

threads mostly short with many bacillary forms; examples of the group are actinomyces farcinicus and the organism obtained in Silberschmidt's case 3.

3. Growth preferably anaerobic; colonies show no mycelial projections, and on solid media are usually small and sharply circumscribed. No growth on gelatin or at room temperature; the colonies are readily crushed and broken up. The organism does not survive as long as those of groups 1 and 2 on artificial media. To this group belong the cultures from six of his human cases as well as those from actinomycosis bovis.

He thinks it too early, however, to attempt a definite division of the pathogenic varieties of the genus actinomyces, and he does not regard pathogenesis as a possible means of diagnosis.

Silberschmidt concludes that:

1. Actinomycosis, contrary to the earlier idea, is not a specific infection caused by a single ray fungus, for a number of different micro-organisms may cause the typical disease picture.

2. The "drusen," which are not always to be found microscopically, may or may not have peripheral clubs, and are colonies which various micro-organisms may form in tissues.

3. The microscopic investigation of the "drusen," or of sections of tissue, permits the finding of the organisms, but not diagnosis of the same.

4. Cultures, which he obtained without difficulty, must be resorted to in order to distinguish the cause of the disease.

5. Mixed infection is not the rule in actinomycosis.

6. It is not at present possible to distinguish by bacteriologic methods between actinomycosis and pseudoactinomycosis.

7. Most of the organisms found in actinomycosis belong to the class of actinomyces, and of this class certain subdivisions are to be made.

Abbott and Gildersleeve[22] have recently pointed out that the various acid-resisting bacilli, distinct from the so-called bacillus tuberculosis, may form mycelial threads with or without typical actinomycotic peripheral clubs, and may cause larger and smaller imflammatory nodules in the tissues of various animals. As is well known, it has been found by Schulze,[25] Lubarsch,[20] Babes et Levadili,[27] Abbott and Gildersleeve,[22] Friedrich and Nösse,[26] and others that various members

of the tubercle-bacillus group and other acid-resisting bacilli, as well as streptothrix eppingeri (Lubarsch), may form branching mycelial threads similar to actinomyces.

Abbott and Gildersleeve urge that these organisms be classed not as bacilli, but under genus actinomyces.

Lehmann and Neumann, in the last edition of their work, classify as actinomycetes all the delicately threaded organisms free from chlorophyll, with true branching, in part very abundantly ramifying mycelium, partly with the formation of conidia. This class is further divided into the coryne-bacteria group containing B. diphtheriæ, B. mallei, B. pseudodiphtheriæ, and B. xerosis; mycobacteria, a group containing B. tuberculosis and the acid-resisting (so called) bacilli in general; and actinomyces, a group made up of actinomyces bovis, actinomyces farcinicus, actinomyces asteroides, actinomyces maduræ, and the various non-pathogenic actinomyces.

It is certain that our organism belongs to the branch of the actinomyces family in which the formation of branched threads without clubs is more or less constant. Its exact position, on account of its failure to grow on artificial media, must remain unknown. Its marked pathogenicity for rabbits serves to separate it from certain forms most commonly met with in the typical actinomyces of man and cattle.

Summary. Actinomycosis of the central nervous system is rare. I am able to find only five (including my own case) primary and thirteen secondary cases. The disease usually affects males in the prime of life; in the primary cases the age being given as twenty-four, twenty-six, and fifty-two years, respectively, in three cases; not mentioned in two cases. In the secondary group, two were sixteen, five between thirty and forty, one forty-three, and one fifty-two years; age not mentioned in four. Two cases occurred in females. Of the primary, three were reported as instances of "streptothrix" infection and only one (Bollinger) was regarded as typical actinomycosis.

Of the thirteen surely secondary cases, eight were regarded as typical actinomycosis, two as probable actinomycosis, two as cladothrix infection, and one as streptothrix infection.

All of the primary cases except one (Bollinger) were acute, while of the secondary in at least ten the lesions of the nervous system were recent, and usually the cause of death.

The organisms were cultivated in two primary (Almquist and Ferré et Fouquet) and in two secondary cases, in one of which (Eppinger's) aerobic and in the other (Sabrazés et Rivière) anaerobic growths were obtained. Eppinger's organism was pathogenic for rabbits and guinea-pigs. In most of the cases neither cultures nor animal experiments were made, the diagnosis being made from the microscopic examination alone. No mention is made of any attempts to test the acid-resisting powers of any of the organisms found. The so-called actinomycotic granules were recognized in the pus of several cases. In one, instead of abscesses there were multiple nodular masses in the brain, and in Bollinger's case there was a firm mass the size of a hazelnut in the third ventricle and in the foramen of Monro. Primary lesions of the lungs and bronchial glands were the most common sources of the metastatic lesions of the central nervous system. In one case the actinomycotic process extended directly through the skull to the meninges and brain.

It seems established that, in the present state of our knowledge, all processes caused by microorganisms having a mycelium of branching, interlacing, and sometimes radiating threads are to be considered as actinomycosis, and that organisms with the above characteristics, whether or not they form "drusen" and clubbed hyphæ in the tissues, are to be regarded as actinomyces.

Further knowledge is necessary before a satisfactory classification of the actinomyces and the processes caused by them is possible. To class tuberculosis under actinomycosis is of doubtful value. It is well to recall, however, that there are two broad divisions of genus actinomyces as used by Abbott and others, the acid-resisting (bacillus tuberculosis and the acid-resisting (so called) bacilli) and the non-acid-resisting or acid-bleaching, and that typical tuberculosis is always caused by the prominent member of the former and typical actinomycosis by the prominent member of the latter group. It is better, with Lehmann and Newmann, to use the term "actinomycetes" for the large number of organisms of the latter group. This acid-bleaching group is apparently a large one, and our knowledge concerning it is best summarized in Silberschmidt's conclusions.

The organism of our case belongs to the branch of this group in which club formation is inconstant or absent, pathogenesis for animals is marked, and cultures on artificial media negative.

Bibliography.

1. O. Bollinger. Münch. med. Wochenschr., 1887, No. 41, S. 789.
2. Almquist. Zeitschr. f. Hygiene u. Infectionskrankheiten, 1890, Bd. viii., S. 193.
3. Ferré et Fouquet. Mercredi Medical, 1895, p. 441.
4. Musser, Pearce, and Gwyn. Transactions of Association of American Physicians, 1901.
5. Ponfick. Die Actinomykose des Menschen eine neue Infectionskrankheiten, Berlin, 1882.
6. Köhler. Berlin. klin. Wochenschr., 1884, Bd. xxi. p. 414.
7. O. Israel. Ibid., 1884, S. 360.
8. Naunyn. Mittheilungen aus der Medizinischen Klinik zu Königsberg, 1888.
9. Keller. British Medical Journal, March 29, 1890.
10. Eppinger. Zeigler's Beiträge zur path. Anatomie, etc., 1890, Bd. ix.
11. Sabrazés et Rivière. La Presse Médicale, 1894, September 22, p. 302.
12. Dolore. Gazette hebdomadaire, May 24, 1896.
13. Martin. Journal of Pathology and Bacteriology, 1896, vol. iii.
14. Chiari. Zeitschr. f. Heilkunde, 1900. Abtheil. f. path. Anatomie, i., S. 351.
15. Flexner. Journal of Experimental Medicine, 1898, vol. iii.
16. Norris and Larkin. Ibid., 1900, vol. x.
17. Lachner-Sandoval. Inaugural Dissertation, Strassburg, 1898.
18. Hektoen. Philadelphia Monthly Medical Journal, 1899, p. 615.
19. Kruse. Flügge's Microorganismen.
20. Lubarsch. Zeitschr. f. Hygiene u. Infectionskrankheiten, 1899, Bd. xxxi., S. 187.
21. MacCallum. Centralblatt f. Bakteriologie, 1902, Bd. xxxi.
22. Abbott and Gildersleeve. Ibid. and University of Pennsylvania Medical Bulletin, June, 1902.
23. Berestenew. Zeitschr. f. Hygiene u. Infectionskrankheiten, 1898, Bd. xxix., S. 94.
24. Silberschmidt. Ibid., 1901, Bd. xxxvii., S. 345.
25. Schulze. Ibid., 1899, Bd. xxxi., p. 153.
26. Friedrich und Nösse. Zeigler's Beiträge zur path. Anatomie, etc., 1899, Bd. xxvi., S. 470.
27. Babes et Levadili. Arch. de Méd. Exp. et d'Anat. Path., 1897, ix., p. 1041.

ACUTE BULBAR PARALYSIS DUE TO HEMORRHAGE AND SOFTENING OF THE PONS AND MEDULLA.

With Reports of Cases and Autopsies.

By CHARLES L. DANA, A.M., M.D.,
OF NEW YORK.

Introduction. The causes of acute bulbar paralysis in all its forms are extrinsic and intrinsic. The *extrinsic* causes are lesions of the cerebral hemispheres, usually double, but sometimes single. These lead to bulbar symptoms, which are usually associated with other symptoms such as hemiplegia, and form what is known as *pseudobulbar paralysis.* Acute ascending multiple neuritis may also lead to bulbar symptoms, and also certain toxic conditions such as paralytic rabies and acute ascending paralysis. Acute bulbar paralysis is also sometimes caused by a purulent meningitis and by caries of the upper cervical vertebræ or of the occipital bone.

The *intrinsic* causes of acute bulbar paralysis are hemorrhages, softenings from thrombus or embolus, acute poliencephalitis, and suppurative encephalitis. In late years it has been found that a good many cases of acute bulbar disturbances, of more or less limited character, are due to inflammatory processes, and literature of recent years contains rather more upon these inflammatory conditions than upon hemorrhages or softenings.

HEMORRHAGE OF THE PONS MEDULLA.

It will be my purpose, however, in this paper to discuss simply acute lesions of the pons and the medulla, due to hemorrhages or softenings. Hemorrhages of the pons are comparatively rare.

The figures given by those who have collected statistics make the range of frequency vary from less than 1 to nearly 10 per cent. on all hemorrhages. The later and more careful statistics seem to show that pons hemorrhages, as compared with cerebral hemorrhages, are not more than 2 per cent. This about coincides with my own experience. Among fifty consecutive cases of intracranial hemorrhage which I personally have seen, only two were pons hemorrhages.[1]

It is interesting to add in this connection that Pitt found, among 9000 postmortems in Guy's Hospital, aneurysms of the vasoartery only nineteen times.

Hemorrhage of the medulla is still more rare than hemorrhage of the pons (only two cases in seventy-five having been reported). I have never seen such a case with autopsy. Of the frequency of thrombotic and embolic softening of the pons and medulla I have no extended statistics. My own experience is, however, that they are more frequent than hemorrhages, and certainly the literature of the subject would show such to be the case. In my own experience the percentage of thrombotic softenings of pons and medulla to cerebral softenings has been about 6 per cent.

Historical. The first communication upon hemorrhage in the pons was made by Cheyne, in his work on *Cases of Apoplexy and Lethargy*, London, 1812; a little later a case was reported by Burdach (1819), and one by Serres in the same year. These individual reports were soon followed by a long series of cases by the French authors: Rochoux, Cruveilhier, Gintrac, Andral, Longet, Ollivier, Durand-Fardel; by the English, Bright, Aber-

[1] Comparative Frequency of Hemorrhages.

Hemorrhage of the brain	30 cases.	
Hemorrhage of the pons	6 "	(Rochoux.)
Hemorrhage of the brain	386 cases.	
Hemorrhage of the pons	9 "	(Andral.)
Hemorrhage of the brain	757 cases.	
Hemorrhage of the pons and peduncles	76 "	(Gintrac.)
Hemorrhage of the brain	153 cases.	
Hemorrhage in the protuberance	21 "	(Durand-Fardel.)
Hemorrhage of the brain	912 cases.	
Hemorrhage of the pons	91 "	(Fagge.)

It is interesting to add in this connection that Pitt found, among 9000 postmortems in Guy's Hospital, aneurysms of the vasoartery only nineteen times.

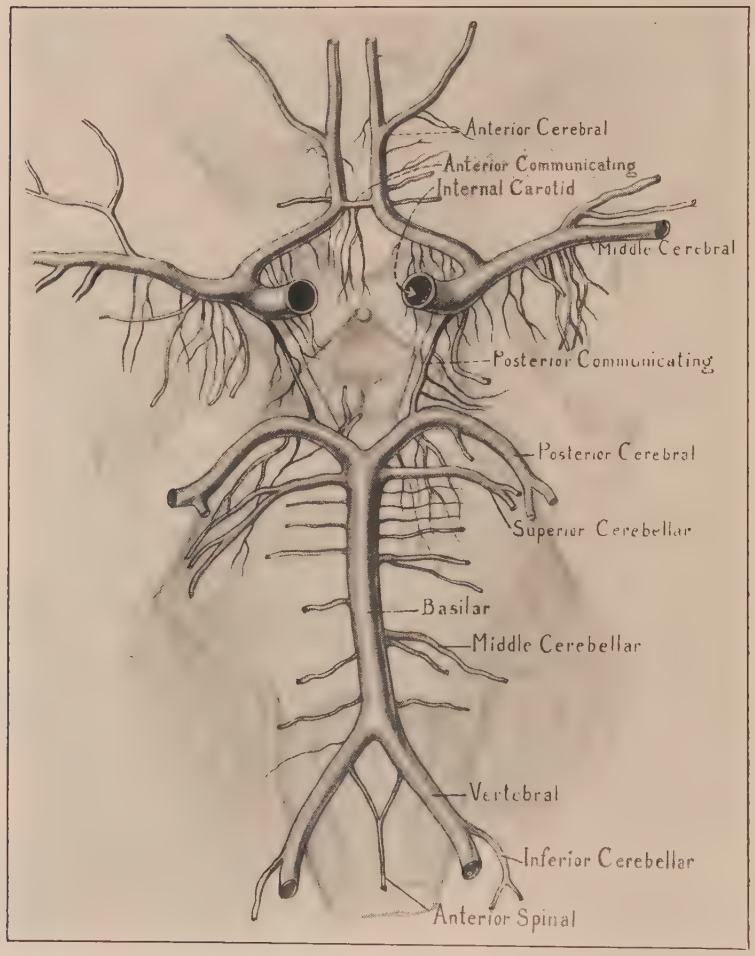
crombie, and Parker ; and by the Germans, Mohr, Romberg, and Bamberger. In 1851 Josias collected a series of fourteen cases. In 1856 Gubler called attention to the diagnostic importance of the so-called "alternate hemiplegia," which has been recognized as characteristic of lesions of the pons. The next most important work upon this subject was by Larcher (*Pathologie de la protubérance annulaire*, Paris, 1868). In 1877 Bode, in an inaugural thesis published at Würzburg, collected the histories of sixty-seven cases and wrote a monograph of much value upon this subject, contributing also several cases of his own. In 1899 Dr. Hans Luce, in *Deutsche Zeitschrift für Nervenheilkunde*, vol. xv. p. 327, collected a series of eighteen cases of pons hemorrhage, and studied them with reference to the question of the convulsions produced by pons lesions.

Since the time of Bode's monograph I can find no extensive or complete contribution to the subject of hemorrhages in the pons and medulla, though there have been a considerable number of special reports and studies.

I have not attempted to present a full bibliography of hemorrhagic apoplexy of the pons or of the acute softening of the pons, but have utilized the statistics of Bode, Larcher, and Luce, and have collected the important cases from that time (1877) until the present.

Points of Investigation. A study of the statistics of the histories of the cases, and of the discussions brought out by them, show that there are a number of points of practical interest which deserve attention at the present time. One of these is the alleged resemblance of pons apoplexies to opium poisoning, a resemblance which has led to a good many mistakes, and is a point which is sometimes of medicolegal importance ; another question is that of the relation of convulsions to diseases or lesions in the pons and medulla ; a third, the question of the frequency and etiology of lesions of these parts ; a fourth, the symptomatology of these lesions, particularly the study of certain special symptoms and syndromes, and the characteristic dissociation of sensibility ; a fifth, the anatomic studies which have been brought out by the investigation of the secondary degenerations from these lesions, and

FIG. 1.



Circle of Willis and arteries at the base of the brain, drawn from specimen prepared for author by Dr. McLean. It shows the relative proportion of the different arteries and the actual number of small and large branches. (Drawn by Shannon.)

by the disturbance of function caused by certain specially localized lesions.

Anatomic and Physiologic. The mid-brain, which includes the cerebral peduncles and corpora quadrigemina; the hind-brain, including the pons, cerebellum, and its peduncles; and the after-brain, or medulla, form a unit which is called the brain-stem. This brain-stem is supplied with blood mainly from the vertebral arteries, which themselves rise from the subclavian arteries and run along a tortuous course within the transverse processes of the cervical vertebræ. Before uniting to form the basilar artery, they give off branches to form the anterior spinal artery and the inferior cerebellar artery, which latter gives off the posterior spinal arteries (Fig. 1). The basilar, which is formed just before the vertebrals reach the ventral surface of the pons, gives off the transverse arteries, the median cerebellar arteries, the superior cerebellar, and the posterior cerebral arteries, all of which may be considered transverse arteries of varying size. All of these vessels give off branches to the cranial nerve nuclei, and nerve roots, and various accessory branches to the gray and white matter. The left vertebral artery is a little larger than the right, and each vertebral artery is a little smaller than the basilar.

The vascular supply of the mid-brain and hind-brain is fairly well differentiated: the vertebral arteries and their branches supply the medulla, with its contained cranial nuclei, namely, those of the eighth, ninth, tenth, eleventh, and twelfth nerves. The basilar artery and its branches supply the pons and its contained cranial nuclei, third, fourth, fifth, sixth, seventh, and eighth nerves. The cerebellum is supplied partly by the branches from the vertebral and partly by branches from the basilar (middle and upper cerebellar). (Fig. 1.)

The nuclei of origin of the third and fourth nerves are supplied specifically by median arteries given off from the upper part of the basilar. The roots of the third and fourth are supplied by root arteries from the same source. The peduncles are supplied by accessory branches from the posterior cerebral. The tubercular quadrigemina are supplied by branches from the posterior cerebral anteriorly, and the inferior cerebellar posteriorly (Duret).

The posterior cerebral artery, though given off usually by the basilar, is essentially a cerebral artery, and supplies the occipital pole of the brain.[1]

The pons and medulla contain, speaking generally, long tracts of nerve fibers which run between the cerebrum and the cerebellum and the spinal cord, transverse tracts which connect the lobes of the cerebellum; various short associating tracts, and, finally, nuclear deposits for the cranial nerves and the various long and short tracts.

The course of the long voluntary motor tracts from the brain to the nuclei of the motor-cranial nerves and to the spinal cord is well known and need not be rehearsed here.

Besides these long voluntary tracts, there are long efferent tracts from the frontal and temporal lobes which end in nuclei in the ventral pons, and thence send fibers to the cerebellum. These frontopontine and temporopontine tracts have probably to do with the automatic co-ordinated muscular movements of the body and extremities.

They are also frontothalamic fibers which have to do, perhaps, with involuntary movements of the face and body in expression, and hence there may be in pons lesions forced laughing and crying.

The long afferent or sensory tracts from the spinal cord to the cerebellum and cerebrum consist of the nerves for cutaneous sensation of touch, temperature, and pain, the nerves of muscle and articular sense (deep sensibility), the nerves of co-ordination and equilibrium.

1. The fibers of the *sense of touch* do not seem to have a definite path. Some cross and some do not in the cord. Some appear to go up in the posterior columns with the muscular sensory tract, while some pass up in the lateral columns. Their exact course in the medulla and pons is not known; they cross in part, seem to go in part with the muscular tract and not with that for pain and temperature; they probably pass diffusely through the formatio reticularis.

[1] According to D'Ostros, the posterior cerebral artery gives off five sets of small branches: (1) to the internal parts of the peduncles, called the internal peduncular; (2) external branches to the external part of the peduncles; (3) arteries of the fissure; (4) arteries of the superior peduncles; (5) arteries of the corpora quadrigemina.

2. The fibers carrying sense of temperature and pain cross in part, at least, in the spinal cord; they ascend in the deep parts of the posterior horns and in the lateral columns (forming part of the ventrolateral tract of Gowers). As they enter the medulla they lie to the outer side of the olivary bodies and pass up in the lateral and dorsal part of the medulla, separated quite a little from the musculosensory tract. As they reach the pons, however, these two sensory pathways get rather closer together. At the upper part of the pons many (and most of the fibers of the Gowers tract proper) curve back through the anterior peduncles of the cerebellum into that organ. Other fibers, however, go through the tegumentum to a nucleus of the thalamus and thence to the sensorimotor convolutions of the cortex.

3. The fibers carrying muscular sensation ascend in the spinal cord uncrossed until they reach the nuclei of the columns of Goll and of Burdach, at the upper end of the cervical cone. The former nucleus receives the fibers from the lower extremity, the latter those of the upper extremity. The fibers then cross in the medulla, forming the sensory decussation. The fibers from the lower extremity cross lower down, *i. e.*, more caudally than those from the upper extremity. They then pass along, forming the interolivary tract (ribbon of Reil) near the raphe or middle of the medulla and between the inferior olives. They tend, as they reach the pons, to spread out laterally, forming a flat band called the lemniscus or fillet. This fillet gradually passes away from the middle line toward the side of the pons, and finally gets near its periphery, ascending into the tegumentum and between the corpora quadrigemina above and the motor tracts below; the fibers continue up, ending in the thalamus and cortex. From the beginning some fibers (arcuate) are sent also to the cerebellum, mostly crossing.

4. The paths for the sense of equilibrium pass up in the direct cerebellar tract and run uncrossed in the corpus restiforme to the cerebellum. Similar fibers representing the equilibrium nerve run from the inferior olive to the cerebellum, also in the corpus restiforme; the fibers of equilibrium from the vestibular branch of the eighth nerve run also in the corpus restiforme.

The position of the foregoing tracts and of the cranial nerve nuclei is shown in Fig. 2.

There is in the medulla a center for the cervical sympathetic fibers; it is perhaps (Onuf, Collins) in a group of cells lying near the solitary bundle. It is, at any rate, near the origin of the vagus and glossopharyngeal. And, as a consequence, in lesions of the medulla, we may get flushing and sweating of the same side of the face, retraction of the eyeball, and narrowing of the palpebral fissure, and contraction of the pupil.

The pulse and respiration are disturbed through injury or irritation of the vagus, but much less in softening than in hemorrhage.

The temperature seems mainly to be affected in irritation and destructive lesions causing compression, such as hemorrhages, and mainly in hemorrhages of the pons.

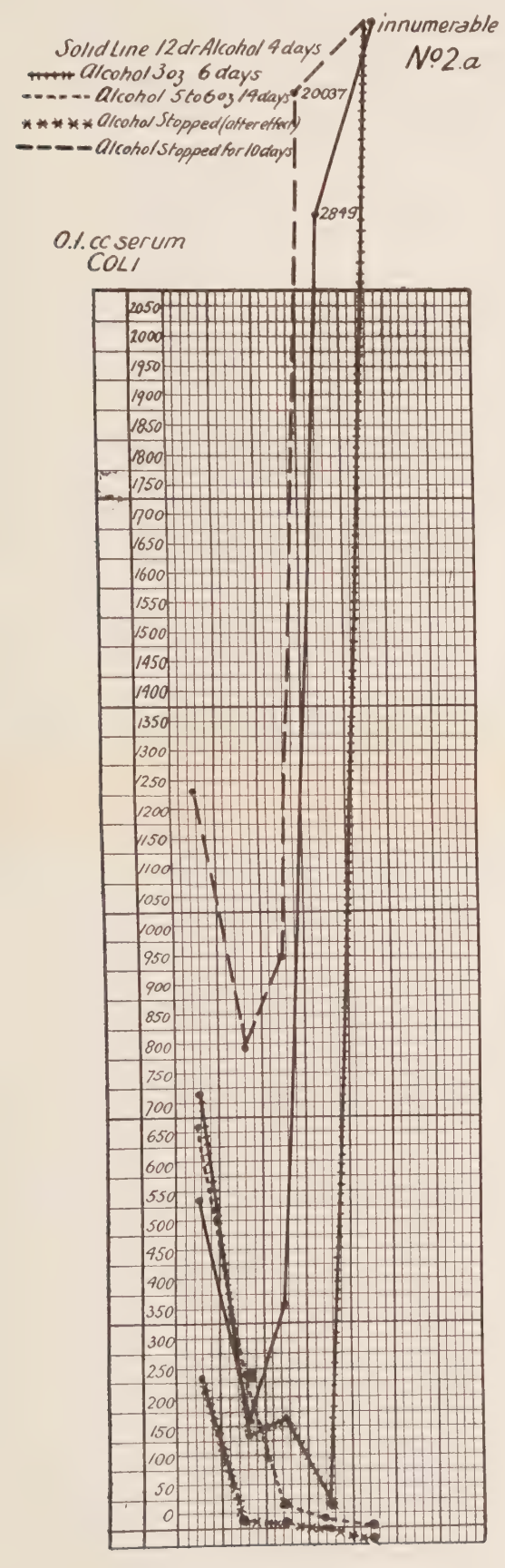
Etiology of Hemorrhage, Sex. Among 46 cases with autopsy, collected by myself, there were, males, 26; females, 20. The statistics of Bode give, males, 40; females, 25; of Larcher, males, 29; females, 15. Total, males, 95; females, 60. The proportion of males to females is therefore not quite 2 to 1.

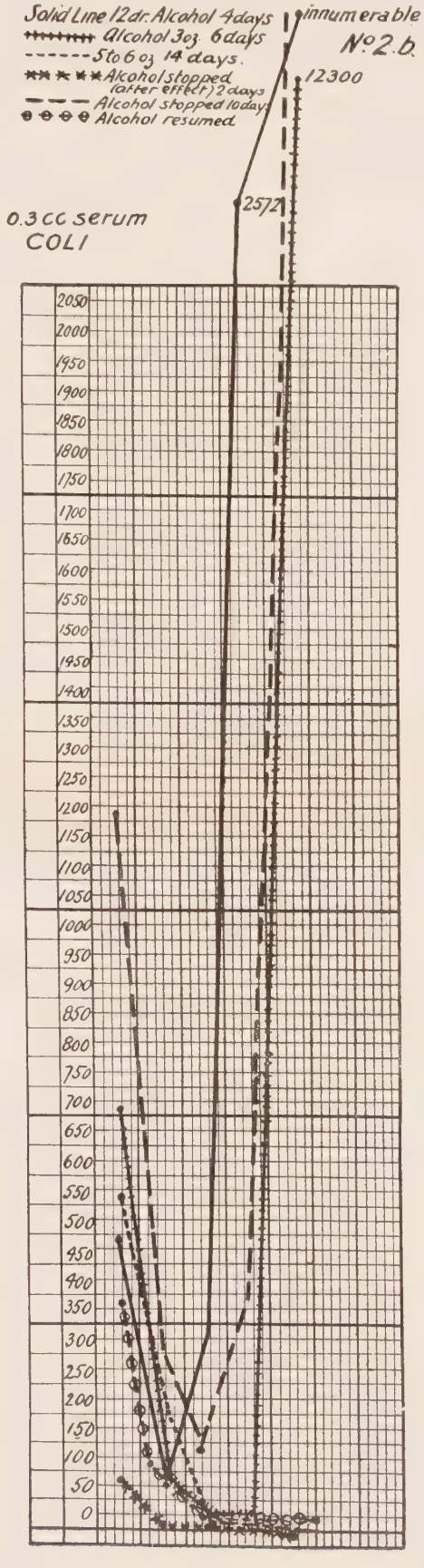
Age. The statistics collected by myself and others give the following:

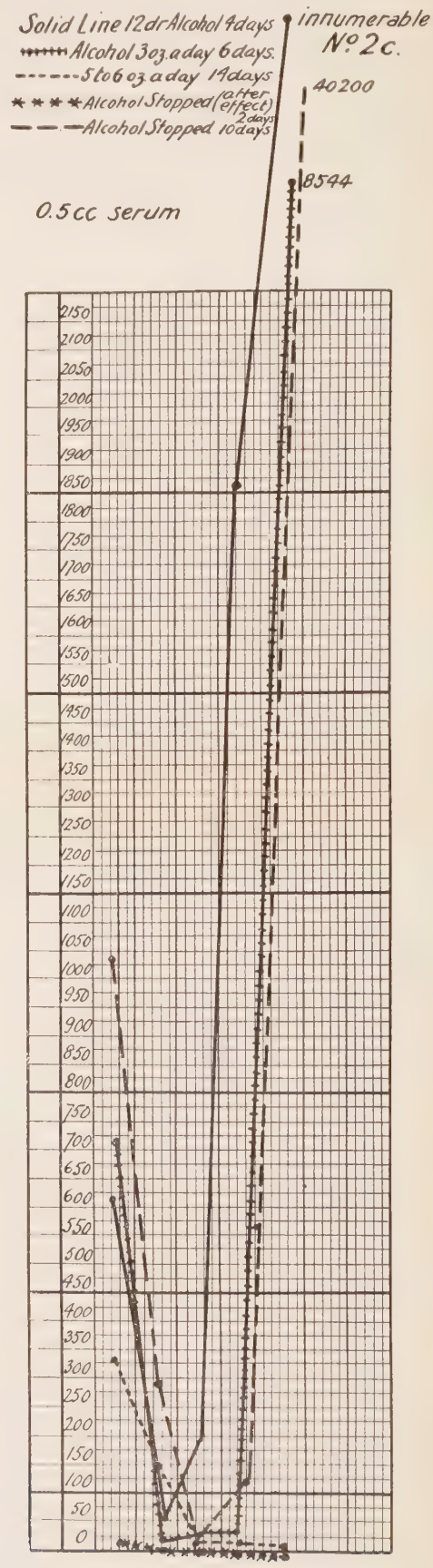
	DANA.	BODE.	LARCHER.	TOTAL.
0–20	2	....	....	= 2
21–30	6	8	14	= 28
31–40	7	10	17	= 34
41–50	15	12	24	= 51
51–60	8	9	3	= 20
61–70	6	10	15	= 31
71	2	10	12	= 24
				190

This shows that one-fourth of the cases occur in the fourth decade of life; next oftenest between thirty and forty, and between sixty and seventy. The cases under twenty occurred, one, at birth, in a difficult labor (Dr. Schultz), and one at eighteen, in status epilepticus. The age range differs from that of cerebral hemorrhage, in that practically no cases occur in childhood.

Other Causes. The most frequent of the determining causes mentioned are nephritis, with cardiac hypertrophy and arterial


Solid Line 12 dr Alcohol 4 days
Alcohol 3 oz 6 days
Alcohol 5 to 6 oz 14 days
Alcohol Stopped (after effect)
Alcohol Stopped for 10 days
innumerable
No 2.a
20037
2849
0.1. cc serum
COLI


Solid Line 12 dr. Alcohol 4 days
Alcohol 3 oz. 6 days
5 to 6 oz 14 days.
Alcohol stopped (after effect) 2 days
Alcohol stopped 10 days
Alcohol resumed
innumerable
No 2.b
12300
2572
0.3 cc serum
COLI


Solid Line 12 dr Alcohol 4 days
Alcohol 3 oz. a day 6 days.
5 to 6 oz. a day 14 days
Alcohol Stopped (after effect) 2 days
Alcohol Stopped 10 days
innumerable
No 2 c.
40200
18544
0.5 cc serum

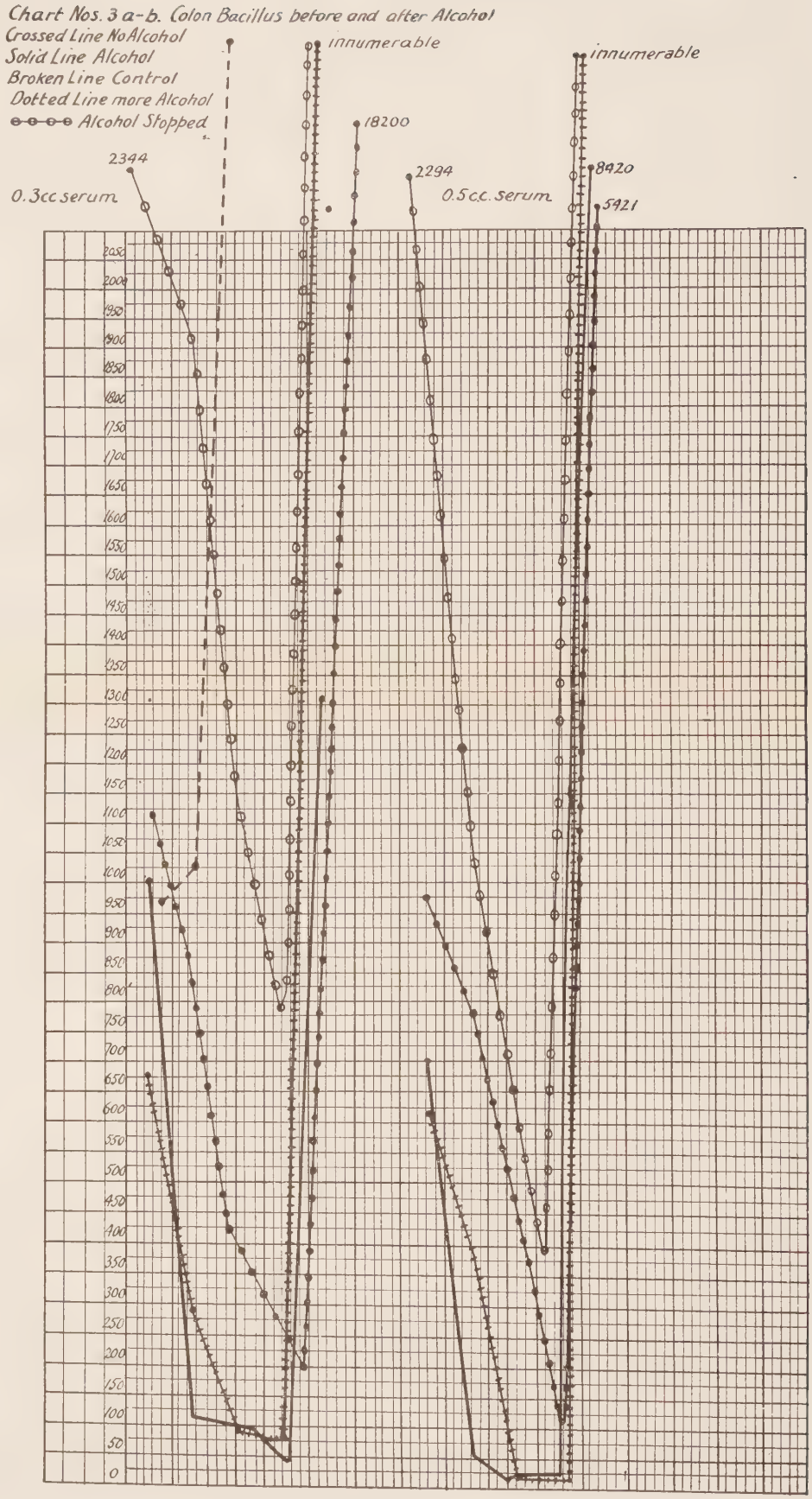


Chart Nos. 3 a-b. Colon Bacillus before and after Alcohol
Crossed Line No Alcohol
Solid Line Alcohol
Broken Line Control
Dotted Line more Alcohol
Alcohol Stopped
innumerable
innumerable
18200
2344
2294
8920
0.3cc serum
0.5cc. serum
5921

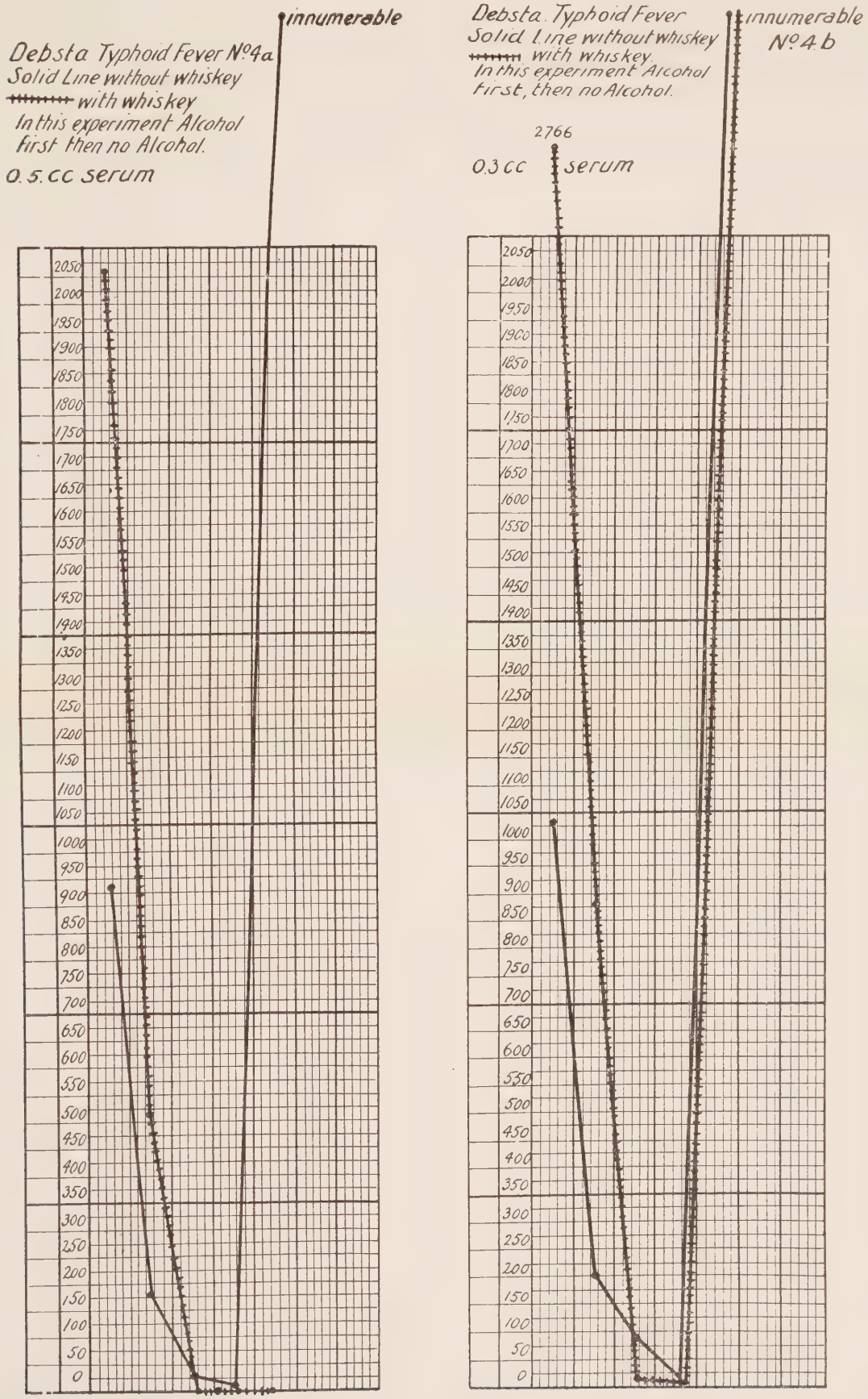

innumerable
Debsta Typhoid Fever No 4a
Solid Line without whiskey
with whiskey
In this experiment Alcohol
first then no Alcohol.
0.5 cc serum
2050
2000
1950
1900
1850
1800
1750
1700
1650
1600
1550
1500
1450
1400
1350
1300
1250
1200
1150
1100
1050
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Debsta. Typhoid Fever
Solid Line without whiskey
with whiskey
In this experiment Alcohol
first, then no Alcohol.
innumerable
No 4 b
2766
0.3 cc
serum

Chart No 5 a. Complement Experiment
Bacillus Typhosus with heated and unheated serum.
before and after Alcohol.
Crossed Line no Alcohol
Solid Line Alcohol.
Dotted Line, more Alcohol.
— — — Complement destroyed
o o o o Alcohol stopped

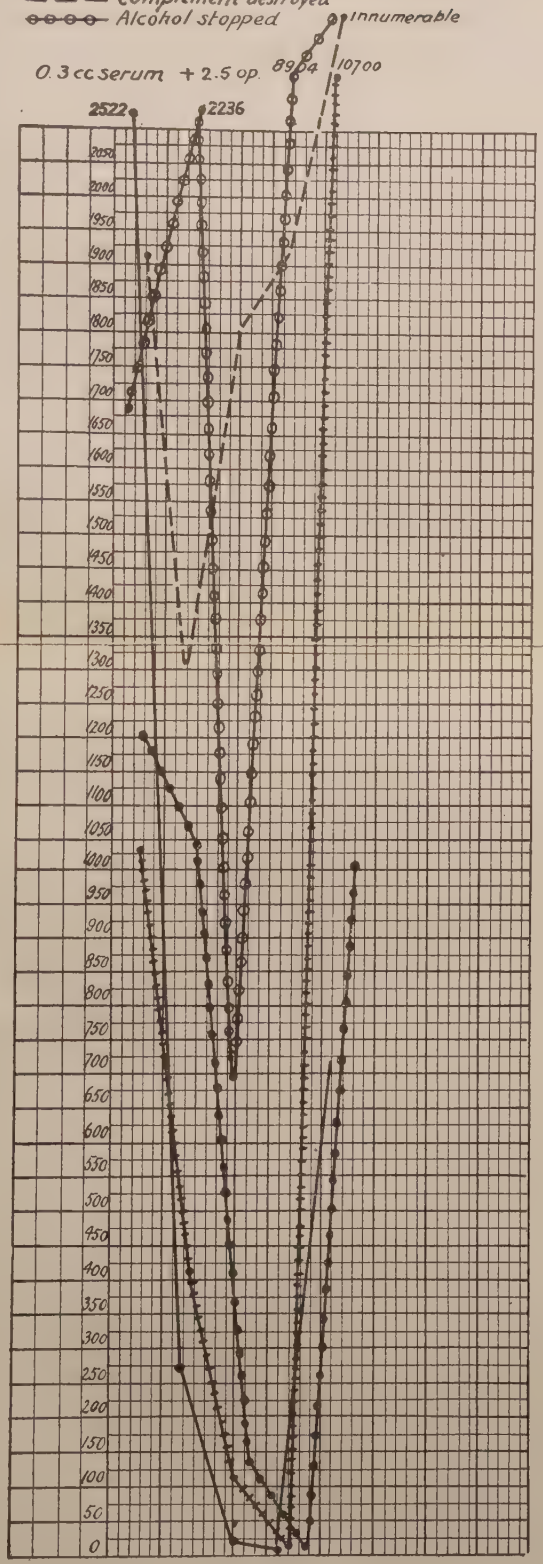
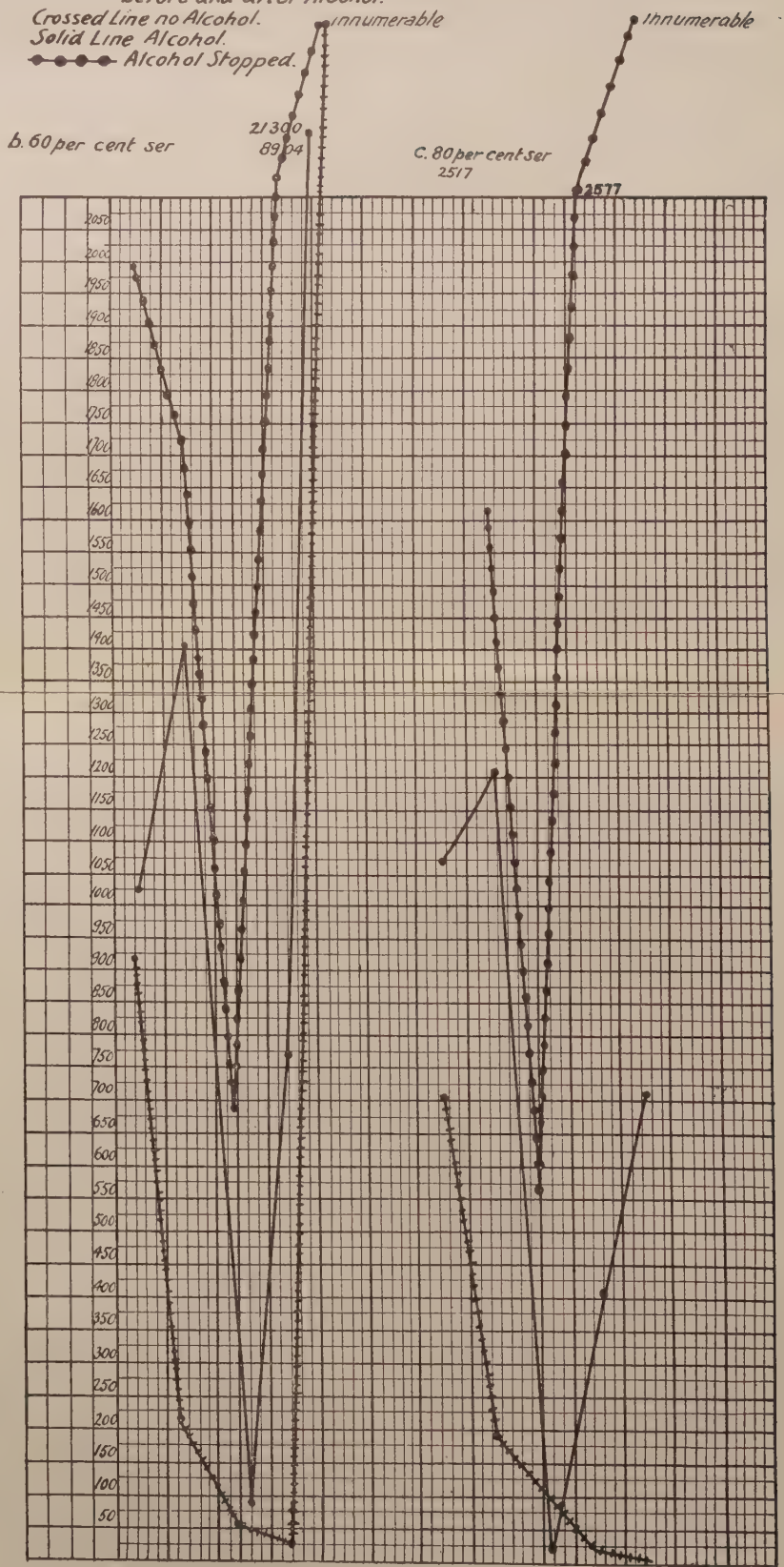


Chart 5 b-c Complement Experiment
Bacillus Coli with heated and unheated serum.
before and after Alcohol.
Crossed Line no Alcohol.
Solid Line Alcohol.
● ● ● ● Alcohol Stopped.



sclerosis. These factors were mentioned fourteen times in forty-four cases. Alcoholism is a concomitant cause, but not very often noted. Syphilis is also rarely observed. Among other causes mentioned are status epilepticus, forceps delivery, caisson pressure, pernicious anemia, gastroenteritis, caries of cervical vertebra, meningitis, and secondary hemorrhage from tumors.

The etiologic factors seem to be much more often those associated with cardiac hypertrophy, arterial sclerosis, and renal disease, and are in the same line as the causes of cerebral hemorrhages. Syphilis seems, however, to be decidedly less often a factor. At any rate, I can find it referred to only three times in forty-six cases. Severe exertion has not been found to be an exciting cause, though it is a disease associated with the laboring classes more than is cerebral hemorrhage. Almost all the statistics are from hospital records. Thus, it may be said in general that those who work more with the fore-brain are more liable to hemorrhages there.

Pathologic Anatomy. The medulla is sometimes somewhat involved in the positive hemorrhages, but I can find only two cases of hemorrhage in this part (Lemcke, Jackson).

Hemorrhages in the pons are apparently usually very severe, but this is due in part to the fact that we base our statistics on cases with autopsy. Probably there are other milder cases which cannot be differentiated from softenings.

	BODE.	DANA.
Large part of pons destroyed	27	12
Focus in or near centre	17	10
More on right side	18	15
More on left side	13	12
Multiple foci	....	5
Capillary hemorrhage	....	3
Pons and medulla	....	2
Large and breaking into fourth ventricle	....	8

Peduncular hemorrhages which may involve some of the pons are not included in these statistics.

Thus, while the earlier statistics of Bode show a large number of severe and total hemorrhages, the later reports show, relatively, more involving only one side. Still, there is no doubt that pons

hemorrhages have a tendency to invade the median parts, and make a large focus of destruction. Fagge states that out of twelve pons hemorrhages five broke into the fourth ventricle.

The arteries oftenest involved are the transverse and median branches of the basilar. The basilar itself is rarely ruptured, nor do we find rupture of the vertebrals or of the posterior cerebrals. There is often found aneurysmal dilatations of these arteries, and the pathologic process is similar to that in cerebral hemorrhage. There is sometimes a basilar aneurysm, and it is probable that by atheroma and thickening the passage of blood into the posterior cerebrals is made less free, and the blood consequently dammed back and thrown into the small arteries of the pons. Atheromatous patches on this artery are often observed, and the transverse arteries develop small aneurysms, as in cerebral cases. In only two of my collected cases was there any associated focus of hemorrhage or softening found, in which respect pons hemorrhage differs from pons softening. Capillary hemorrhages were found in three of my collected cases—one of pernicious anemia, one the case of status epilepticus, and one in a woman, aged sixty-one years (Cohn). Durand Fardel reports a case in an old woman, and several others have been reported. Such cases belong more properly to acute softenings. Multiple foci of hemorrhages occur rarely. More than two were reported in five cases (Raymond, R. Ronnell, Urain).

Symptoms. The only type of pons hemorrhage which can be really described as having a characteristic *syndrome* is that in which the hemorrhage is severe, either involving a large part of the pons, or breaking into the fourth ventricle, or both. The smaller hemorrhage causes symptoms which partake, in a measure, of the typical cases, but shade off into types resembling the acute softenings.

It has to be remembered that about one-half of all pons hemorrhages are severe and typical, that the medulla is usually spared, or is, at least, not primarily involved, and that the posterior cerebrals which supply the peduncles and the occipital lobes are rarely involved in hemorrhages. The pons itself, then, is the part most injured. Besides the motor, sensory, and transverse cerebellar

tracts, it contains in its dorsal part the nuclei and fibers of origin of the fifth, sixth, seventh, and eighth cranial nerves. In almost any severe lesion we would expect involvement of the fifth (trigeminal) and sixth (abducens) nerves; if high up, involvement also of the third (motor oculi); if low down, involvement of the eighth (facial), eighth (acoustic).

Only when the medulla is involved would we expect serious involvement of ninth (glossopharyngeal), tenth (vagus), eleventh (spinal accessory), and thirteenth (hypoglossal).

It is not my purpose to go minutely into the analysis of the symptoms here. The general history of an attack is somewhat as follows: The patient has some prodromal headaches and malaise for a few days, with vertigo, and sometimes vomiting. Then he falls suddenly, as if by a lightning stroke, into a coma, usually very profound. There are twitchings of the face or of the limbs, or both, but rarely any general convulsion (three cases). The face is flushed, there is a fall of temperature, and the pulse is irregular, but not markedly increased or slowed, as a rule; the respiration is slow, 4 or 6 per minute, or more often irregular, and of Cheyne-Stokes type. The pupils are contracted to a pinpoint, and do not respond to light, but may be uneven. There is convergent strabismus or conjugate deviation of the eyes. The limbs are at first stiff, but may be relaxed later and the reflexes increased.

The patient cannot be aroused, but can be made to vomit. A few hours later the temperature rises, sometimes very high—106° to 108°—but usually not. There are involuntary movements of the bowels; swallowing is impossible; evidences of dyspnea are shown. The pulse becomes more rapid, cyanosis develops, the patient dies in six to twenty hours, usually with evidence of paralysis of respiration.

If the hemorrhage is less severe, the coma is less profound, or may be absent, the patient shows signs of agonizing suffering and difficulty in respiration, evidences of crossed paralysis, crossed anesthesia, and disturbance of equilibrium and ataxia can be noted.

In still smaller lesions we find no such severe general symptoms, but only those due to a circumscribed focus in one side of the

pons, because the smaller lesions are unilateral. The syndrome of pons lesions then is:

1. Headache, malaise, vomiting.
2. Sudden and profound coma.
3. Twitching of the face and limbs, or both.
4. Myosis and convergent strabismus or conjugate deviation (away from the side of the lesion).
5. Slow, irregular breathing.
6. Irregular pulse.
7. Dysphagia.
8. Paralysis of limbs or crossed paralysis and exaggerated reflexes.
9. Gradual rise of temperature, sometimes to high point.
10. Death inside of twenty-four hours.

The *prognosis* in severe pons hemorrhage is very bad, death occurring, as already stated, in a few hours. What proportion of all cases get well I cannot say, but as most of the cases of acute bulbopontine apoplexies which recover give a history pointing to softening, it is probable that a great majority of hemorrhages are fatal.

Reports of Cases.

Case I. *Hemorrhage of the Pons.*—Pauline K., aged twenty-four years, German, admitted to Bellevue Hospital February 17, 1898. Family history negative. Denies all syphilitic history. About three weeks previous, while menstruating, some water was thrown over her and the menses were stopped. She then began to have fainting spells, from which she would soon recover. After having had several of these attacks her speech became affected. Then she began to have trouble in using her left arm, and later her left leg, until she became completely paralyzed on the left side. When the patient was admitted to the hospital she seemed well nourished, with flushed face, tongue dry and coated, and breath offensive. She was restless and apathetic and in a semistuporous condition. The pulse was regular, about 116, respiration 24, temperature 99.5°. The lungs were normal, and the heart had a faint systolic murmur at the base. The left arm was paralyzed and the left leg rigid; the right side of the face was paralyzed. There was some difficulty in swallowing and some indistinctness in speech. The epigastric reflexes were absent. Wrist- and elbow-jerks increased more on the right side; knee-jerk increased, slight ankle clonus, but the reflexes were difficult to determine in the left leg owing to its rigidity. The conjunctiva of the right eye was congested. The face was flushed and there was marked dermographia. There were constipation and retention of urine.

On the 18th paralysis of the right facial was present and the eye could not be closed. There was some paralysis of the right external rectus; the pupils were small and responded to light, but the reaction was slow. The temperature on this day had fallen to 98°, the pulse was 106, and respiration 28. The urine was 1025, acid, no albumin, no peptones; urea, 0.014. The temperature had gradually increased on the 18th, until at noon it was 100¾°, and on the morning of the 19th gradually rose to 105⅗°, the pulse rising to 140 and the respirations to 32 and finally to 44. The patient grew more stuporous and had four slightly convulsive attacks, during which she frothed at the mouth. These attacks were not, however, apoplectic, but rather accesses of rigidity, with staring of the eyes. She died on the morning of the 19th, two days after admission. No evidences of anesthesia could be obtained, and the symptoms consisted, therefore, of a paralysis of the sixth and seventh nerves on the right side, and paralysis and rigidity on the left, with dysarthria and dysphagia, slight convulsive attacks and further high terminal temperature.

An autopsy was made by Dr. Harlow Brooks, and it was noted on the autopsy that the left pupil was smaller than the right. I omit items not connected with the nervous system, or of special importance with relation to this case.

The heart was practically normal; the arch of the aorta showed slight endarteritis, and the coronary artery very slight endarteritis. The caliber of the carotid arteries appeared somewhat diminished in size. The abdominal and thoracic viscera practically normal, and showed no signs of syphilis.

The bloodvessels at the base of the brain were intensely congested, and in places contained thrombi.

The pia mater was thickened and opalescent over the frontal convolutions; the basal ganglia congested, but there was no lesion in the cerebral hemispheres.

Just to the right of the median line in the anterior portion of the pons is found a hemorrhagic area, 1 to 2 cm. in diameter, extending back through the pons until it occupied almost the entire right side of pons and extends in area to left side, extending backward, becoming narrower, until it finally terminated in posterior surface of pons, left side. The vessel of left side—the tissue of medulla and cervical segments of cord and cerebellum—were apparently normal. The center of involved area contains a clotted mass, evidently surrounding a small bloodvessel, and a small artery leading into involved area at anterior portion of pons was found, the lumen of which is plugged. Pituitary gland usual size.

Case II. *Hemorrhage of the Pons.*—The patient, a man, aged about fifty years, was brought to the hospital suffering from vertigo headache. While walking along the ward on his entrance to the hospital he suddenly fell down in deep unconsciousness and almost immediately expired. No history could be obtained of him. On autopsy a large hemorrhage was found in the pons near the raphe. No notes were taken at the time, and the case has little except statistical interest.

ACUTE SOFTENING OF THE PONS MEDULLA.

History. After Duchenne had in 1860 described the malady known since then as progressive "glossolabiolaryngeal palsy," attention was drawn to bulbar palsies of other types and due to other causes. Griesinger (1862) and Lebert (1866) collected and reported cases showing that bulbar palsies might be due to local aneurysms and to softenings from other vascular diseases. Joffroy, in 1872, emphasized the distinction between degenerative or protopathic palsy and palsies from other causes; further contributions were made by Hallopeau (*Thèse de Paris*, 1875), Lichtheim (*Deutsche Archiv für klinische Medicin*, Band xviii.) and Nothnagel (*Diagnosis*, 1879). In 1885 Oppenheim and Siemerling (*Charité-Annalen*, vol. xii.) described the different forms of acute bulbar palsy and pseudobulbar palsy, and they gave a bibliography and short analysis of the important cases of acute softening reported up to that date. The cases which I have studied include some not mentioned by these last authors, and most of those reported since their article, including my own.

Nearly all the cases utilized in drawing conclusions were reported with autopsy; but there have been some very careful studies made on clinical cases, which have much value, for it is comparatively easy to make the local diagnosis, at least in pons-medulla lesions.[1]

Etiology. Among thirty-nine collected cases with autopsies, four being personal observations, I found males, 27; females, 11; showing a ratio of over 2 to 1 in favor of the male sex. In acute softening the proportion of males is greater than it is in hemorrhage.

The age relations are shown in the following table:

1–30	= 0
31–40	= 9
41–50	= 10
51–60	= 7
61–70	= 3
71	= 4
	33

[1] A very complete bibliography of bulbar diseases of all kinds is given by Van Oordt, Deutsche Zeitschrift f. Nervenheilkunde, 1896, vol. viii. p. 137.

There are no records of acute softening before the age of thirty. The favorite age is between thirty and fifty, during which period most of the softenings are luetic. In old age they are due more to senility and degenerative changes in the arteries.

Among the other causes lues was found in 11, arterial sclerosis in 9, nephritis and arterial sclerosis in 14, cardiac disease in 14, alcoholism in 1, senile atheroma in 2.

No doubt lues plays a greater part than is shown here, while the arterial changes associated with alcoholism, nephritis and cardiac hypertrophy are less prominent than in hemorrhage. In two cases the patients were insane, and in three other cases the patients were in the early stage of general paresis. In two cases the patients had locomotor ataxia, local tumors, and aneurysm of the vertebral arteries were found in two cases. Schlesinger (*Zeitschrift für klinische Medicin*, 1896, No. 32) mentions three cases caused by sudden lowering of atmospheric pressure on coming out of a caisson.

No special exciting causes could be made out.

It appears to me that excessive work and worry in anemic and poorly nourished women lead sometimes to bulbar apoplexies.

The great cause of acute bulbar softenings in early and middle life is syphilis. The attacks are not rarely premonitory of an impending tabes or paresis ; they indicate that the disease has a rather serious hold on the nervous system, and are of more importance than the casual cranial-nerve palsies due to meningitic exudates.

In old age softenings occur because there has been a particularly serious degree of atheroma and sclerosis of the bulbar vessels. What determines it we do not know, but, as I said of hemorrhage, it seems that hard manual labor combined, perhaps, with anxiety seems to lead to pathologic changes in the vessels of the brain.

Symptoms. The prodromal symptoms of acute bulbar softening are generally those of an endarteritis and of a syphilitic invasion of the brain. In a small proportion of cases (about 20 per cent. in my statistics) there has been, some months or years previously, thrombosis of a cerebral artery, and, consequently, cerebral hemiplegia. The prodromal symptoms then are occasional preliminary

attacks of hemiplegia, vertigo, numbness in the limbs, headache, temporary speech disturbances, and double vision. Just before the attack in particular the patient may suffer from vertigo, noises in the ears, hoarseness, vomiting, and headache. The Stokes-Adams syndrome may be present (Brissaud). The attack may also be preceded by symptoms of nervous agitation, and even of slight mental disturbance, especially in the luetic cases.

The seizure itself is usually sudden, and within a half-hour, or an hour, is very nearly complete, usually being accompanied with headache, vertigo, and perhaps vomiting. In other cases the symptoms may come on in two or three successive slight attacks, continuing over several days.

After the attack the patient is affected with symptoms depending upon the situation of the lesion. In practically all cases, however, there are two sets of phenomena: first, the bulbar symptoms, and, second, some form of sensory or motor hemiplegia. The bullar symptoms consist of oculomotor palsies, a facial or trigeminal paralysis, or both, disturbances in the equilibrium, vertigo, roaring in the ears, difficulty in speech and deglutition. There is rarely any change in temperature. The pulse may be slow or irregular. The hemiplegic symptoms consist of a paralysis, usually, but not always, on the side opposite the cranial nerve involved, so that there is an alternating or crossed hemiplegia, associated with some form of anesthesia.

The symptom groups in pons-medullary lesions may be of three types:

1. The syndrome of medullary softening. The lesion is of the inferior cerebellar or vertebral of some of their branches.

2. The syndrome of pons softening. The lesion is of some of the transverse branches of the basilar.

3. A general syndrome, including symptoms seen in lesions of both pons and medulla, or in lesions in which the focus, while lying mainly in one part, extends into the other. The lesion is a thrombosis or embolism of the vertebral, just as it joins the basilar, and leading to some occlusion of the basilar.

1. *The Syndrome of Medulla Softening.*—When the medulla chiefly is affected with focal softening, it is due usually to a

thrombosis of one of the vertebrals. It may, however, be due to lesion of the inferior cerebellar artery, or of a small branch of this artery or the verterbal. The symptoms vary with the extent and locality of the lesion, but there is a general group which is certainly more common than any other, and which may be said to characterize softenings in this area. These symptoms are:

Disturbances of speech and of swallowing.

Hemiplegia.

Disassociation of cutaneous sensations, there being an anesthesia to pain and temperature, but not of touch, upon the affected side.

Ataxia, involving either the arm or leg, or both, of the side opposite the paralysis. This ataxia is due to loss of deep sensibility, and there is defective sense of position and astereognosis.

With the ataxia, or perhaps without it, there may be what Babinsky terms *asynergy*, that is to say, a loss of the co-ordinating activity of the volitional impulses, so that one segment of the limb is moved without harmonious action with the other. This condition would ordinarily be classed as a form of ataxia.

There is a condition of forced movements, or tendency to fall to one side (lateropulsion).

There is often, though not always, an evidence of paralysis of the sympathetic upon the side of the lesion, shown by a contraction of the pupil upon that side, a diminution in the size of the palpebral fissure, with retraction of the globe, and some congestion of that side of the face. Besides these rather typical symptoms, we often get some paralysis of the tongue, from involvement of the twelfth nerve, and some disturbance of the heart action. There may be, also, involvement of the trigeminus through injury of the descending root, vertigo, and noises in the ears, possibly deafness, and there may be even a facial palsy upon the side opposite the hemiplegia, though this is more common in pons lesions. Some disturbance, also, may occur in the oculomotor nerves, especially the sixth, through involvement of the nucleus of that nerve and of the posterior longitudinal bundle. Convulsions and spasmodic movements are not observed, nor forced laughter and weeping. The lesion is sometimes so extensive as to involve somewhat both sides of the medulla, and then there

may be motor and sensory disturbances upon both sides of the body. The importance of the foregoing group of symptoms has been especially emphasized by Babinsky (*loc. cit.*).

2. *The Syndrome of Pons Softening.*—Lesions in the pons are most apt to be in the ventral part, near the raphe, and next to this, in the dorsal part of the pons, from involvement of a branch of the basilar artery.

Lesions in the pons have no such single characteristic syndrome as those in the medulla. There are some very clear-cut cases in which there is paralysis of the fifth or of the seventh nerve upon one side and hemiplegia upon the other (crossed hemiplegia), but this type of case is not by any means the most frequent. Lesions in the pons may occur without any involvement of the cranial-nerve nuclei, except those connected with deglutition and, perhaps, of speech (Case I.). When they occur in the ventral region there are necessarily disturbancse of motility, shown by hemiplegia, by irritative motor disturbances, such as twitchings, and sometimes by forced laughter or weeping and morbid emotional states.

When the lesions are deeper in, reaching nearly to the floor of the fourth ventricle and the gray matter, we begin to get involvement of the sensory tracts, and to have hemianesthesias. These hemianesthesias are usually also those of pain and temperature only, and thus *disassociation of sensibility* is characteristic also of pons lesions.

When the nerve nuclei are involved it is almost always the nuclei of the motor nerves of the eye and of the trigeminus. So that we may get oculomotor palsies, with some trigeminal disturbance upon one side, and hemiplegia, with or without anesthesias, upon the other.

There are in pons lesions also vertigo, disturbances of hearing, and some cerebellar symptoms, but not so often the forced movements that we see when the posterior cerebellar peduncle is involved in strictly medulla lesions. In pons lesions high up the fifth and seventh nerves may be involved on the same side as the hemiplegia. In pons lesions, *dysarthria is more often absent* than present. Thus, Makowski collected eighteen cases of one-sided

lesion and found dysarthria absent in ten. In general, then, the absence of involvements of the cranial nerves, from the eighth to the twelfth, the absence of marked sensory troubles, except of the fifth nerve, the *presence of forced laughter* and weeping, motor irritability and the involvement of the oculomotor nerves and of the fifth nerve, would suggest a pons lesion.

The abdominal and skin reflexes are often feeble. Sometimes there is a great deal of pain from irritation of the fifth nerve, and sometimes the pupil may be dilated.

It is possible to have a pons lesion simulating almost exactly a cerebral hemiplegia (Case III.), but this is extremely rare. If there is evidence of a bulbar lesion, and there is not a crossed paralysis, the lesion must be high in the pons.

3. *The Syndrome of Pons-medullary Softening or Acute Softening of both Pons and Medulla.*—The symptoms here are really only an extension of the type of medullary softening, the lesion being, as stated, usually a thrombosis which involves the vertebral at its junction with the basilar. The syndrome is a fairly definite one, but mainly so in that it is an enlargement of the picture seen in pure medullary lesions.

Thus we have :

(1) Hemiplegia ; (2) pain-temperature, anesthesia on the same side as hemiplegia ; (3) loss of deep (muscular) sensibility, with ataxia, often on opposite side to hemiplegia ; (4) lateropulsion to side of lesion ; (5) paralysis of various cranial nerves, especially seventh to twelfth, on the side opposite hemiplegia,(6) dysphagia and dysarthria ; (7) paralysis of sympathetic on same side as lesion, with myosis and retraction of globe ; (8) subjective sensations of vertigo, roaring in ears, pararthria and pain ; (9) disturbances in rhythm of pulse and respiration.

STUDY OF SPECIAL SYMPTOMS OF ACUTE PONS-MEDULLA SOFTENINGS.

Hemiplegia occurred in a little more than one-half of the observed cases, and may be more accentuated in the arm or leg, usually in the arm. Occasionally, with hemiplegia upon one side, there is some

weakness of the side opposite, that is, on the same side as the lesion. Hemiplegia with an ocular palsy is oftenest seen; hemiplegia with crossed facial palsy is relatively rare, while hemiplegia with involvement of the fifth nerve is more frequent. Thus, in relative frequency we have hemiplegia and eye palsies, hemiplegia and fifth-nerve palsies, and hemiplegia and seventh-nerve palsies. Hemiplegia is almost always accompanied with anesthesia, and this anesthesia is on the same side as the paralysis. In sixteen cases with hemiplegia there was anesthesia on the same side in eleven, on the side opposite in one. The hemiplegia and anesthesia are often accompanied with disturbances of muscular sense and ataxia, and this disturbance is somewhat oftener on the opposite side from the paralysis, *i. e.*, on the side of the lesion. In five cases of hemiplegia with ataxia, the ataxia was upon the same side as the hemiplegia in two, and on the opposite side in three. The type case is hemiplegia, with pain-temperature anesthesia on one side and some ataxia on the other.

Convulsive Movements. The view originally exploited by Nothnagel, that there was a convulsive centre in the pons, is not confirmed by clinical and pathologic experience in man. In lesions of the pons there are practically never any convulsions, due, at least, directly to this lesion. When the onset is quite acute, and the softening involves the ventral part of the pons and the fibers of the motor tract, there may be some trembling and twitching, as in the case reported in this paper. (Case I.)

As regards the convulsions in hemorrhages of the pons, an exhaustive study was made by Luce, who was able to collect, however, only one case in which convulsions occurred. But in spite of this he is led to conclude that the nuclei in the ventral part of the pons are epileptoginous. There is no doubt that in the acute injuries of the pons, when the ventral part is involved, twitching and tonic spasms occur, involving the face and extremities, with sometimes tremors, but these do not amount to actual convulsions, and it must be borne in mind that in the cases where convulsions have been observed, the patients had not perfectly normal brains; that is to say, they were suffering from arterial sclerosis, nephritis, and possibly uremia or paresis.

Forced laughter and crying have been noted in three cases besides my own (Bechtereff, Ransohoff, Mills).

It is well established (Kirchhoff, *Archiv für Psychologie*, Bd. xxiv., Heft 3) that there is in the thalamus a center which controls the emotive expression of the opposite half of the face, so that when this is destroyed, though the patient can move the face voluntarily, it remains immobile in laughing or crying. It may be supposed, then, that when this center is cut off from its control by the cortex there may be involuntary laughter or crying. This center must be in connection with lower bulbar centers for the motor nerves of expression (seventh, eleventh, twelfth, third cervical, etc.), and it must to an extent inhibit and control the bulbar mechanism. The movements, however, in crying and laughing are originally purely under bulbar control. (I have reported the case of a baby which lived five days and cried continuously; it had only a spinal cord, medulla, pons, and cerebellum, with the merest rudiment of a thalamus.) Hence it can be understood that when certain pathways from cortex or thalamus to the bulb are cut off or irritated, the bulbar centers for producing movements of laughing and crying may be loosened from control and go off in explosions; just as there are exaggerated reflexes, trepidations of the limbs, etc., when the voluntary motor path to the limbs is destroyed, and explosive laughter is like an exaggerated reflex, a trepidation, or an ankle clonus.

Oculomotor Symptoms. Some involvement of the motor nerves of the eyes occurs in about one-fourth of the cases. In pons-medullary lesions it is the sixth nerve and its associated branch from the third to the internal rectus that are oftenest affected. When a serious degree of ophthalmoplegia occurs it means a higher and peduncular lesion. In ordinary pons-medullary lesions, then, we find as the common symptoms: conjugate deviation, paralysis of conjugate deviation, internal strabismus, convergent strabismus, nystagmus.

The old formula that in cerebral lesions the eyes turn away from the paralysis and toward the lesion, while in pons disease it is the reverse, has a very limited application. In cerebral lesions when there is great pressure or very large destructive lesion, the

conjugate involvement of the eyes is toward the lesion and away from the side paralyzed, but more often in cerebral lesions there is only enough disturbance to irritate the central tracts to the abducens of the opposite side and the internal rectus of the same side, and the eyes consequently turn away from the lesion.

In pons lesions when there is conjugate deviation away from the lesion, it is due to irritation of the central path. More often one sees simply paralysis of conjugate deviation toward the side of the lesion. This is due to a paralyzing lesion of the central path to the abducens. Sometimes there is a convergent strabismus due to lesion of both abducens. If the sixth nerve root is affected we have simply an external strabismus. Nystagmus is often seen in pons, and rarely in cerebral lesions. This is due to various causes, but perhaps chiefly to lesions of the central segmental tract, or of the posterior longitudinal bundle, two tracts which are concerned in the co-ordination of the eye muscles and in bringing them into relation with the other cranial nerves.

The contraction of the pupils which occurs in pons hemorrhages must be ascribed mainly to the compression and irritation of the third-nerve nuclei; and, perhaps, to a coincident palsy of the sympathetic center.

Sensory Symptoms, Pain, and Paresthesia. Pains referred to the parts supplied by the sensory tracts are rarely present. Patients complain sometimes of headache, and occasionally of some burning pains or cold pains, but pure neuralgic pains, except those due to an occasional irritation of the fifth nerve, are very infrequent.

Paresthesias, on the other hand, are quite common. The sense of numbness and pricking is usually present in the anesthetic limb or side. Cold pains and burning sensations also occur, and are referred to the anesthetic parts. The discomfort from these is sometimes very great. In hemorrhages of the pons, when the roots of the trigeminus have been torn up, there is at times great agony from this cause, but I find that central pains from lesions of the pons and medulla, other than those due to irritation of the trigeminus, are very rare. It seems to be a general physiologic law that only irritation of the peripheral sensory neuron causes pain. The central pains which are sometimes described as occur-

ring in brain disease are extremely rare, and it is a question whether they are not, after all, psychic. Even paresthesias are much less common from lesions of a central sensory neuron than from lesions of the peripheral nerve.

The anesthesias which occur in the pons and medullary softenings are peculiarly distinctive. The anesthesia is characterized by the fact that it involves more or less perfectly the tract for pain and temperature, and not for touch or muscular sense. Among twenty reported cases I find hemianesthesia affecting pain and temperature, or else temperature alone in eighteen of the cases. Tactile anesthesia, however, is occasionally present; it may be on the same side with the pain-temperature anesthesia, or it may involve both sides. In two of my cases there was involvement of the temperature sense alone, and in one case this affected only the cold sensations. In one case the temperature anesthesia occurred upon the left side, while there was a temporary hemiplegia upon the right.

The usual motor-sensory syndrome in pons-medullary lesions would be a hemiplegia, with pain-temperature anesthesia upon the side of the paralysis, and muscular anesthesia (ataxia), either upon the same side or upon the opposite side, more often the latter.

A good many cases are reported with anesthesia of the face on the same side as the hemiplegia and anesthesia of the body. Here the lesion must be in the upper half of the pons, above the decussation of the cerebral tract to the trigeminus.

Hemianopsia is in rare cases observed in pons lesions. It would occur oftener, probably, if the posterior cerebral were not so readily supplied by blood from the posterior communicating. Besides, pons softenings usually are due to lesions of the basilar near its origin from the vertebrals.

Disturbance of deglutition is due particularly to involvement of the deglutition center, which lies in the motor root of the vagus (*nucleus ambiguus*). A disturbance of deglutition can be produced when only one side is involved.

Disturbances of speech (dysarthria) are almost always present, and may be due not only to lesion of the vagus-glossopharyngeal nuclei, but to the upper motor path to these nuclei in the accessory

lemniscus; also to injury of the root fibers of the vagus.[1] This nucleus sends motor fibers to the larynx (Dees).

Dysarthria is an important symptom when due to paralysis of the vocal cords, since the presence of such a palsy excludes pseudobulbar palsy.

Vertigo is a very common and often distressing symptom in pons and medulla lesions. It may be confounded by patients with the disturbance of equilibrium caused by lesions there, and often the two things go together. Vertigo of a very marked type is due, most often, to a lesion of the *corpora restiformia*, but it is also produced probably by lesions involving the nucleus and central paths of the vestibular nerve.

Lateropulsion or forced movements to one side, usually to the side of the lesion, occurs in lesions involving the *corpus restiforme*, the tract from the inferior olive to the cerebellum, or the middle peduncle of the cerebellum.

Reflexes. If the motor tract is seriously involved we get an exaggeration of the deep reflexes, but in other cases these are not particularly disturbed. Usually the abdominal reflexes are either feeble or abolished.

Temperature, Pulse, and Respiration. The temperature is usually normal or slightly raised.

The pulse may be slow, but is usually irregular and rapid.

The respiration, unless the lesion is severe, is usually not much disturbed. Disturbances of the respiration, temperature, and heart rhythm are due to involvement of the vagus and its nucleus (Van Oordt, *loc. cit.*).

Paralysis of the larynx is due, according to Dees, to involvement of the central nucleus of the ninth and tenth nerves.

Paralysis of the sympathetic may occur in either pons or medullary lesions. It causes reduction of the palpebral fissure, slight retraction of the globe, myosis, reddening, and perhaps sweating, on the side of the lesion.

A systolic blowing sound heard over the mastoid is sometimes heard in arteriosclerosis of the vertebral with aneurysmal dilatation

[1] Van Oordt. Deutsche Zeitschrift f. Nervenheilkunde, vol. viii. p. 210.

as it passes into the basilar. This is due, according to Wallenberg, to stricture of the vertebral, causing increased pressure in the carotid.

Pathologic Anatomy. On this subject I have nothing new to offer, and shall speak but briefly. The lesion is almost always an endarteritis, usually of syphilitic origin, but sometimes due to other causes and associated with alcoholism and nephritis, and old age. In senile cases, like Case IV., there is only a very extraordinary degree of atheroma and senile thickening. Not rarely aneurysmal dilatations are found on the vertebral or basilar arteries.

The following statistics show that the left side is more often affected. The basilar artery and the pons are slightly more often affected than the medulla. The *most common lesion* is a thrombosis of the vertebral with secondary thrombosis of the posterior part of the basilar. Thrombosis of the anterior basilar, as occurred in Case I., is very rare. I find notes of but one other case.

Simple senile softening of the pons, as in Case IV., is also very rare. I find one case besides my own (Leyden).

Location of Lesion in Softening. The main seat of the lesion was: in the medulla, 13; in the pons, 19; in the pons and medulla, 7.

The lesions in the medulla were: on the right side, 5; on the left side, 8; in the pons, on the right side, 6; on the left side, 10; near the middle, 3. This shows a special preponderance for the left side. The arteries mainly affected were:

	Right.	Left.	Total.
Inferior cerebellar	3	4	7
Basilar			12
Vertebral	1	7	8
Both vertebrals			2
Multiple			2
Associated softenings in the cerebrum were observed in			10

The basilar is usually soon involved by extension when a thrombosis occurs in the vertebral. The vertebral thrombosis may lead to thrombosis of the inferior cerebellar secondarily.

Embolism is very rare. Hallopeau and Leyden report cases.

Comparison of Acute Hemorrhages and Softenings in the Pons Medulla. The medulla is rarely affected by hemorrhages.

Softenings affect the medulla and pons about equally; pons and pons-medulla softenings are twice as frequent as medulla lesions alone.

In non-syphilitic cases a lesion confined to the pons is rather more apt to be hemorrhagic than softening, especially if it be severe and occur in connection with nephritis and arterial sclerosis, whereas a lesion of the medulla is practically always a softening. Both hemorrhages and softenings occur in men about twice as often as in women. Softenings occur rather earlier in life than hemorrhages, and are more frequent also in old age. Hemorrhages are relatively rare from fifty to sixty, while softenings do not drop off to the same extent.

Syphilis is a very much commoner factor in softenings, being present in over one-third of my cases, and probably is much more frequent than this percentage indicates. Arterial sclerosis, cardiac hypertrophy, and nephritis are the prominent causal factors in hemorrhage; the last two factors are rarely noted in softenings, except in extreme age. We would expect hemorrhages, perhaps only capillary, in a bulbar paralysis, developed in connection with pernicious anemia, caisson accidents, status epilepticus, and childbirth.

Hemorrhages have usually fewer prodromata; the onset is more sudden, and the conditions more severe, and the prognosis more serious. Twitchings and convulsive movements, profound coma, contracted pupils, and serious respiratory disturbances belong to hemorrhages rather than softenings. Hemorrhages occur almost entirely in the hard-laboring and hospital classes. Softenings are met with in all grades of society.

Personal Cases.

Case I.[1]—*Syphilitic endarteritis and thrombosis of basilar artery; softening.*

Summary.—Male, aged thirty-two years. Prodromal headache and emotional irritability; sudden development of vertigo and left hemiplegia; later,

[1] This case was examined by me and shown to my class. The notes and diagnosis were made by Dr. J. R. Hunt, who also made the histologic examination and notes.

right hemiparesis, tremblings of limbs, forced crying and laughter, roaring in ears, dysarthria. Later complete anarthria, glossoplegia, and dysphagia; no sensory symptoms, temperatare normal, pulse 120. Death. Autopsy: Thrombosis of anterior basilar and softening of anterior pons in its ventral part only.

[By Dr. Hunt.]

The patient, J. L., was a young man, aged thirty-two years, Canadian, cigarmaker by occupation, single, family history negative. He used alcohol in moderation, tobacco in excess. In January, 1899, contracted syphilis, with mild secondary cutaneous manifestations and general adenopathy. Received seven weeks' dispensary treatment and all symptoms disappeared. In June, 1901, he became very much depressed; would burst into tears over trivial causes. At this time he also had headaches and was generally weak and run down. The headaches continued with intermissions and increased severity until December, 1901, when he was forced to discontinue his work for three weeks. One year before this his eyes had been so weak as to interfere with reading. He received internal treatment at an eye clinic, where he was told the affection was syphilitic in character. On January 18, 1902, while at work, he was seized with sudden weakness and vertigo and was unable to speak for half an hour. A few hours later he became completely paralyzed on the left side. This improved on the succeeding day, when the right side became paretic.

Was admitted to Bellevue Hospital, January 19, 1902, and walked into the ward, the left arm visibly paretic; while his bed was being prepared the left leg became completely paralyzed. He would burst into paroxysmal fits of weeping every few minutes. He complained of very severe headache and vertigo, roaring in the ears, and some difficulty in articulation. Temperature 98.6° F., pulse 120, respiration 28. Urine negative.

Status on admission, January 19, 1902: Good physique, well nourished, moderately anemic. Is in a very emotional state; in attempting to answer questions or perform simple acts consequent upon the examination he is subject to *spasmodic attacks of crying;* sometimes this weeping will be turned suddenly into laughter. There is general tremor involving the head, extremities, and tongue, more especially on the left side. It is coarse, jerky, and irregular, not intentional in character, and resembles (but in a very exaggerated form) the tremblings accompanying a severe chill. His mind is clear and memory unimpaired. There is complete left-sided hemiplegia, including the lower branches of the left facial, and deviation of the tongue to the left. Marked rigidity with ankle and wrist clonus and Babinsky reflex on the left side. Skin reflexes are absent.

The right side is paretic; the tendon reflexes are exaggerated; Babinsky reflex present; skin reflexes present. Except for a moderate dysarthria, speech is unimpaired. The pupils are equal, all reactions present. Ocular excursions normal. Examination of thoracic and abdominal organs negative.

January 24th. Sudden loss of power of speech. Could only utter inarticulate sounds.

26th. Status: The patient is conscious and carries out simple orders. Pupils are equal and respond promptly to accommodation, feebly to light; ocular excursions normal; no nystagmus. Movements of the jaw are very week and feeble; the mouth can only be partially opened. The tongue cannot be protruded beyond the teeth. Swallowing of liquids is accompanied with coughing and regurgitation through the nose. On attempting to swallow, the larynx scarcely moves. Cannot articulate a single word; hears watch-tick on the right but not on the left. Incontinence of urine for twenty-four hours (inability to call). The right side is weak, but the limbs can be moved. Ankle clonus present; no Babinsky. Pain sense is keen on both sides. Breathing is irregular in rhythm. Pulse is rapid and compressible.

27th. Respiration rapid and shallow; pulse rapid and feeble; unconscious; died at 8 P.M.

Autopsy. The basilar artery from its middle to the junction of the posterior cerebrals is converted into a white, rounded cord; the other vessels of the circle of Willis are normal to the naked eye. (Fig. 3.) The larger vessels arising from the basilar, *i. e.*, the posterior cerebrals and the superior cerebellar, are distended with blood, but the walls are normal. There is swelling and softening of the pons on its basilar aspect, especially on the right side. Small patches of fatty degeneration on the intima of the thoracic aorta; heart normal; no hypertrophy. Old tuberculosis (healed) with adhesions at both apices. Hypostatic congestion of both lungs. The other organs, save for moderate congestion, are normal. No gummata found.

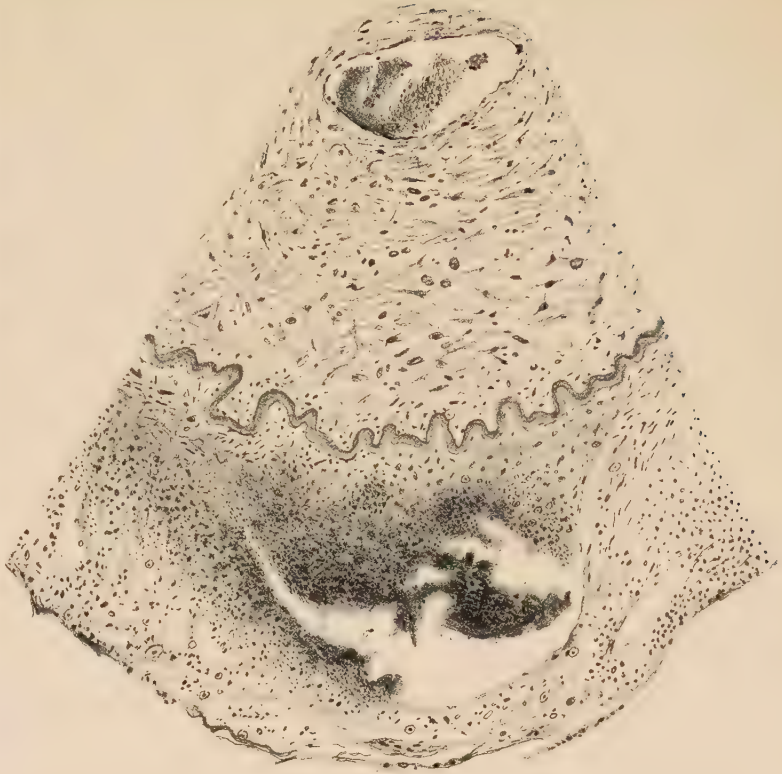
Histologic Examination Serial sections were made of the affected portion of the basilar artery. There was a very high grade of concentric endarteritis, and the lumen was almost (but nowhere completely) occluded. (Fig. 4.) It contained an old thrombus, composed of fibrin, inclosing a few white and red cells. The thickening of the artery is essentially an endarteritis, but the media and adventitia are extensively infiltrated with round cells. In one portion of the adventitia extending into the media is an area of necrosis with epithelioid, but without giant cells (gumma). (Fig. 4.) The anterior cerebrals and middle cerebrals, save for a slight round-celled infiltration of the adventitia, are normal. The choroid plexuses contain many corpora amylacea, but the vessels are normal. The small central arteries of the thalamus and the cerebellum are likewise normal. Transverse section of the velum interpositum shows round-celled infiltration of the adventitia in a few of the larger vessels.

Marchi sections of the cord show an absence of the secondary degenerations, the paralysis not having been of sufficiently long standing. In the upper half of the pons is an area of softening, greater on the right than on the left side, and situated in that portion traversed by the pyramidal tracts. The median and lateral fillet are untouched. The medulla and lower pons, save for a moderate round-celled infiltration of the pia and congestion of the

FIG. 3.

Base of brain, showing thrombosis of the basilar artery.

FIG. 4.



Section of basilar artery, showing endarteritis and small gumma of the adventitia.

Fig. 5.

Transection of pons, showing areas of acute softening limited to the ventral and motor parts.

vessels, are normal. There is one minute perivascular hemorrhage in the medulla. Nuclei of the cranial nerves are normal. (Fig. 5.)

The lesion extended upward to the upper limit of the pons, so that it could still be just seen on section made at this level. Below it extended to below the middle of the pons. There was no lesion in the cerebral hemispheres and cerebellum or the spinal cord.

Remarks. Thrombosis of the cerebral half of the basilar artery is very rare. I find only one other case recorded; hence, in a measure, the peculiarity of the symptoms. Hemorrhages, however, are not infrequent in arteries branching from the middle and upper portions. The total anarthria would exclude a pseudobulbar palsy.

The case is of further interest in demonstrating that a complete occlusion of the anterior portion of the basilar may affect only the central portion of the pons, the cranial nerve nuclei and net-fibers and the sensory tracts remaining intact, the collateral circulation received through the posterior cerebrals and the lower basilar having sufficed to maintain the nutrition of these parts.

The more characteristic symptoms of a positive lesion—as alternate paralysis of the fifth, sixth, and seventh nerves, conjugate deviation or paralysis of the conjoint movements of the eyes, myosis, hyperpyrexia, convulsions, sensory disturbances, forced movements, and oculomotor symptoms—were absent throughout.

Hence a differential diagnosis from a double capsular lesion—*i. e.*, a pseudobulbar paralysis—was by no means easy. The severity and constancy of the emotional outburst, and the peculiar, coarse, general tremor, however, were in favor of a pons localization.

In view of the unusual findings in the medulla, the bulbar palsy must be referred to a lesion of the fiber tracts in the pons carrying motor impulses from the cortex to the cranial-nerve nuclei.

Case II.—Summary: Male, aged forty-eight years. Emotional excitement, dysarthria and hoarseness, dysphagia; later delirium.

Right side: some tactile anesthesia, pain anesthesia, some ataxia, slight hemiparesis. Left side: small palpebral fissure, marked ataxia of arm.

Autopsy. Thrombosis of left vertebral at junction with basilar artery. Softening in left pons. Small spot of softening in right medulla.

The patient was a steward on a steamer. He had always enjoyed good health, and was said to have been a sober and temperate man. Three or four days before his admission to the hospital he was confined to bed and

apparently very sick. He was occasionally delirious and complained of having a severe cold, having some difficulty in articulating, which was probably due to the beginning thrombosis. It was stated that he used to be a very heavy man, weighing over 200 pounds, but that he had in the last six months been reduced in flesh to 130 or 140 pounds. He had complained during this time of a partial paralysis of his left arm and of a cough. When the patient was admitted his mind was in such a condition that he could give no trustworthy account of himself. The appetite was fair, though he had some general bronchitis. He talked very hoarsely, as though there was some difficulty with the muscles of the larynx. When he drank anything a little fluid entered the larynx, causing violent coughing.

Examination made on his admission to Bellevue Hospital, February 28th, showed a man quite stout, with some degree of conjunctivitis of the left eye. The left palpebral fissure was smaller than the right. There was no evidence of any marked paralysis of the arms or legs. There was some loss of pain and locality sense along the whole right side below the spine of the scapula; the contact sense is not diminished. There is also on the right side a marked ataxia of the leg, and the patient on this account was unable to walk unaided or to stand alone. There was, perhaps, with this ataxia, some motor weakness, but it was difficult to determine. On the left side there is a marked ataxia of the movements of the arm. There was, therefore, an ataxia and anesthesia of cutaneous sensation for pain and locality upon the right side, and on the left side marked ataxia of the arm. There was some little disturbance in articulation, and a distinct difficulty in deglutition; the larynx was not examined.

The patient became, in the next two or three days, delirious and excited. His ideas were extravagant, he always felt first-rate, and he had, to a certain degree, delusions of grandeur. The patient had no fever, pulse continued good; urine was high-colored, acid, 1030; no sugar or albumin; the temperature ranged from normal to 99.5°; pulse was about 100. He died very suddenly on the morning of the fifth day after admission.

Autopsy. The brain was congested, the meninges thickened and opaque. There was considerable bloody serum in the lateral ventricles. The membrane on the floor of the fourth ventricle was thickened. The arteries at the base were thickened and somewhat atheromatous. The basilar artery showed the presence of an aneurysm of the size of a pea at its junction with the two vertebral arteries; the vertebrals showed an endarteritis. The left vertebral artery was plugged, there was a softened spot in the left side of the pons extending to the middle peduncle of the pons and in the left side of the medulla near the dorsal surface; also a softened area in the posterior part of the optic thalamus; ependymitis of the lateral ventricles. The lungs showed spots of lobular pneumonia; the heart, fatty degeneration and atheroma of the aorta. There were some appearances over the front of the legs suggestive of syphilis.

The brain was lost before it could be further examined, but there were two lesions—one in the right pons and the other in the left medulla.

Case III.—Thrombosis and softening of right side of ventral pons.

Summary. Male, aged seventy-four years, no previous history; sudden left hemiplegia with some rigidity; face on same side involved. Emotional irritability, no forced laughter or crying, slight sensory disturbances. Softening in right side of ventral pons.

The patient, Orlando V., married, aged seventy-four years, American, was admitted to Bellevue Hospital on May 26th, without any previous history except that he had been found suffering from hemiplegia. He was a large man, quite senile in appearance, but not emaciated.

The mind was clear, but he seemed rather childish and was restless and impatient, grasping his paralyzed hand and continually asking when he would get well. There was no dysarthria or trouble with swallowing. There was a paralysis of the left side of the body of the ordinary type, *i. e.*, the lower face was moderately affected, the upper face was hardly at all. The left arm was quite helpless, the leg somewhat less so; he could not walk, but he could draw up the leg and move the arm a little. The eye muscles were not affected. There was some rigidity of the left arm and leg; the knee-jerks and elbow-jerks were lessened on the left and normal on the right. There was flexor response in the left foot, but not in the right. Epigastric reflexes not present. There seemed to be a very slight obtunding of cutaneous sensibility to pain on the left leg and arm. The urine had to be drawn with catheter. It had specific gravity of 1020, albumin and hyaline casts. Pulse on admission, 72; respiration, 20; temperature, 97⅕° F., rising next day to 99⅘° F. The heart was large and there was a slight systolic murmur at the apex. The arteries were hard; the pulse, however, of rather weak tension. The temperature continued 98° and 99° F. On the ninth day it was taken twice in each axilla.

Right axilla, 97.2–97.4; left axilla, 97–97.4, showing no essential difference.

The patient continued to become more restless; he complained of no special pain, and did not have any fits of crying or laughing. He slept badly and had to be given morphine at times at night. He continued to grow weaker; his mind became more confused and dull. He passed feces involuntarily. There was no change in his paralysis; no spasmodic symptoms developed. He died June 13th of exhaustion, eighteen days after admission.

Autopsy. The vessels at the base were whitened and thickened with atheromatous changes to an extraordinary degree, but there was no complete obliteration of any of the vessels.

On palpation the right ventral surface of the pons was felt soft, and transections show that there was a softened area involving the ventral part of the pons through nearly its whole length. The softened area was largest in the upper half of the pons, where it involved the deep transverse fibers and the motor tracts and pons nuclei. The lesion became slightly smaller posteriorly, and at the level of the medulla the tissue was firm and apparently normal. The softening was limited entirely to the motor part of the pons and did not

involve the superficial transverse fibers nor those of the trapezium. The softening was white and not so pultaceous as to fall out when sections were made. No specially obliterated vessel was found. On the corresponding ventral left half of the pons there was a small recent hemorrhage about the size of a pea. The medulla was normal.

Case IV. *Thrombosis of pons, crossed hemiplegia, paralysis of left trigeminus and right half of body.*—Male, aged thirty-six years; previous history negative, except that he had drank moderately and had been active in athletics. Denied absolutely ever having had syphilis. He suffered from eczema, and was treated for this by Dr. George H. Fox, with whom I saw the case. In August he noticed a feeling of numbness upon the left side of the face, but this was not accompanied by any other marked symptoms. On November 30th he became a little dizzy and went to bed feeling well. Next morning he awoke paralyzed on the right side, in the arm and leg, and on the left side of the face. Seen by me the next day, he showed a moderate facial paralysis of the left side, a marked paralysis of the right arm, less of the leg, and a complete anesthesia of the left side of the face and left half of the mouth and tongue as far back as the pillars of the fauces. The uvula hung straight. The muscles of mastication on the left side were slightly affected. He had some dysarthria, but no trouble in swallowing. There was some paresthesia on the right side, but no anesthesia, and no form of objective sensory disturbance. There was no loss of sense of taste in the anesthetic side of the tongue, and no apparent disturbance of mucous or salivary secretion. The left eye showed slight myosis.

The patient gradually improved, but a month later he had another slight attack of hemiplegia, attacking mainly the left arm.

Case V. *Crossed hemiplegia, paralysis of left trifacial and right side of body, with anesthesia.*—Sebastian K., aged sixty years, German. The patient was admitted to Bellevue Hospital without previous history. The patient had the marks of advanced senility; his mind dull, and had some difficulty in speech. There was complete paralysis of the right upper extremity, partial paralysis of the right lower and total paralysis of the left side of the face. The skin reflexes were absent on the paralyzed side; deep reflexes present; sensation to pain was diminished on the paralyzed side. Patient became more and more apathetic, and suffered from incontinence of urine and feces; bed-sores developed. Death; no autopsy.

Case VI. *Cerebral syphilis, thrombosis of branch of right vertebræ, right hemiplegia, thermoanesthesia, paralysis of left vocal cord; later, general paresis.*—C. H., aged thirty-nine years, married. The patient had always been a strong, vigorous man, but he had indulged in alcohol a good deal, and had been infected with lues eight years before I saw him. About a year before my examination of him he had an attack of right hemiplegia and right thermoanesthesia, with a paralysis of the arytenoids, so that he had some difficulty in speech. The patient was sent to me by Dr. Holbrook Curtis, who made an examination of the larynx, and furnished me with this diagnosis. The laryngeal paralysis was on the left side. He recovered entirely from the

hemiplegia, and when I saw him had simply a loss of the heat and cold sense upon the right side of the body; some of the laryngeal paralysis was still present; no ataxia. There were exaggerated reflexes, but no ankle clonus or extensor response of the toes. In other words, the effects of his attack were nearly gone. It was evident, however, that he had a slight softening in the left side of the medulla. He subsequently developed paresis and died in about two years.

CASE VII.—*Summary:* Male, aged forty years, syphilis, incipient tabes, sudden development on *right side* of ataxia, tactile anesthesia, analgesia of lower face, paresthesia of heat, paresthesia of cold in lower face, slight hemianopsia; no paralysis. *On left side:* Analgesia and thermoanesthesia, paresthesia of cold; no cutaneous anesthesia; no paralysis. No dysarthria or dysphagia; no lateropulsion. Lesion probably in lower half of left pons.

The patient had a luetic infection at the age of twenty; for the past five years he had suffered from lightning pains in the legs; for one and a half years the bladder had been slow. A year ago he had an attack of grip, followed by left facial herpes. About nine months before I saw him he had an attack of right hemitaxia, with no disturbance of speech or loss of consciousness, or difficulty in swallowing. He was obliged to remain in bed a month on account of awkwardness of the right side; along with this disturbance on the right side he had a loss of pain sense on the left side and over a spot on the right side of the chin. His condition of analgesia and ataxia improved, but he suffered from subjective sensations of heat on the right side, and of freezing cold pain over the left side of the face.

When seen by me he had rigid pupils and slight right hemianopsia, which he said came on at the time of his attack. The knee-jerks were exaggerated. He had lightning pains and the visceral weaknesses of posterior sclerosis. Physical examination showed him to be a person in good general health, able to walk fairly well, with no hemiplegia or motor paralysis. There was ataxia of the right side, shown by inability to place the finger at a definite point or recognize the position of the limbs, but there were no forced movements. He had at the time of his attack some right tactile anesthesia, but never any motor paralysis. There was anesthesia to heat and cold on the left side of the arm, trunk, and leg, and slight analgesia over the same area; also an analgesic spot on the right side of the face in the distribution of the inferior branch of the fifth nerve. He had allochiria; that is, on pinching the left side of the body, he would feel it on the right side at a corresponding point. His right hemianopsia appeared more marked in damp weather, and when he was tired. The ataxia is only moderate. He could use the hand clumsily, could put the finger fairly well to the tip of the nose, recognize weights and the position of the limb, and it is mainly a defect in motor co-ordination. He has the Brauch-Romberg symptom, but can stand with the eyes closed and feet wide apart. There is a slight tremor in the right hand. His left thermoanesthesia was absolute. Even freezing solutions cause only pain, and hot things the same. He had a slight analgesia on the left side, and he did not feel a strong electric current. Co-

ordination of the left side was perfect. He had had no disturbance of speech, of deglutition, or of the tongue. He had a drooping of the right lid, but the ocular movements are normal. There were some tickling and paresthesia of the left side of the face where he once had herpes. The left pupil was larger than the right, but reacted to light. He had a hyperhidrosis of the left hand.

I infer that this patient must have had a thrombosis affecting the medulla, involving the median and outer lemniscus and parts external on the left side.

Case VIII.—Female, aged fifty-two years; two healthy children. The patient had been subjected to much worry for the past two or three years. Habits good, no infection. One week ago had a very severe headache; late in the day slight ptosis. Walked home and went to bed. In two days this was nearly well. Then the ptosis returned with involvement also of the left eye and thickness of speech, but no hemiplegia. She again went to bed and gradually became semicomatose. In the last two days she had Cheyne-Stokes respiration.

When examined by me the patient was in bed, unconscious, though she could be partially roused at first. She put out her tongue and moved her hands, arms, and legs fairly well and co-ordinately. She had Cheyne-Stokes respiration. Pulse, 106; regular. She had complete double ptosis. Both pupils were dilated and did not react to light. The right eye turned out, the left was straight. All ocular movements paralyzed; all other cranial nerves seemed normal, except that she had difficulty in swallowing and that her speech was thick. Knee-jerks were exaggerated; slight clonus, more on right. Babinsky present on both sides. Epigastric reflexes gone on both sides. No anesthesia. The patient died three days later.

Case IX. *Syphilitic endarteritis and thrombosis of branch of upper basilar, right hemiplegia, thermoanesthesia, with ataxia of left arm.*—Male, aged forty-four years; lived an active life, participating in outdoor sports, and had always been temperate. About eight years before I saw him he had an infection which was thoroughly treated. Six months before I saw him he had a slight attack of hemiplegia on the right side, with thermoanesthesia of the left side. There was also a slight ataxia of the left arm.

When seen by me he still had some traces of the right hemiplegia, but could walk fairly well. There was still complete thermoanesthesia of the left side and a very slight trace of ataxia in the left arm. No hemianopsia. He subsequently suffered for one or two years from general symptoms of arterial sclerosis of the brain, but gradually improved. He had at times a slight right hemianopsia.

Thus the symptoms were: right side, hemiplegia (temporary); left side, thermoanesthesia (permanent); slight ataxia (temporary).

Bibliography with Notes.

Hemorrhage of Pons and Medulla.

Bristowe. Transactions of the Pathological Society of London, 1890, vol. xi.
Charton. British Medical Journal, January 26, 1895.
Cohn, M. Archiv f. Psychiatrie, 1901, vol. xxxiv. p. 616 (two cases, one of capillary hemorrhage and of cerebral thrombosis).
Dutil. Société Anatomie, etc., Paris, 1887.
Echner. Journal of the American Medical Association, June 24, 1899.
Eichorst. Jahrbuch des Wiener Krankenhauses, 1902, p. 626.
Gee and Tooth. Brain, 1898.
Glaser. Allgemeine medicinische Centr. Zeitung, 1900, p. 1186 (collection of sixteen cases).
Goodman, P. T. Lancet, 1900, p. 1067 (with rupture of heart).
Gouget. Bulletin de la Société Anatomie, etc., Paris, 1894.
Jackson. Lancet, 1872 (hemorrhage in left medulla).
Joffroy. Archives de Physiologie, 1886.
Kahler and Pick. Präger Vierteljahresschrift, p. 79.
Lechre. Bulletin de Société de Anatomie de Paris, November 25, 1898, p. 683 (case with general convulsions).
Lemcke. Deutsche Archiv f. klin. Medicin, 1884, xxxiv. (hemorrhage in left medulla).
Lenoble. Revue de Médecine, 1897, No. 6, p. 425 (case in pernicious anemia).
Leyden. Klinik der Ruckenmarkkrankheiten, vol. ii. p. 65.
Lloyd, J. H. The Polyclinic, p. 529.
Luce. Deutsche Zeitschrift f. Nervenheilkunde, 1899, vol. xv. p. 335 (with chronic convulsions and pons hemorrhage below lemniscus).
Marfan. Société Anatomie de Paris, 1887.
Maygrer and Chavane. Revue Neurologique, 1900, vol. viii. p. 241.
Meyer, P. Archiv f. Psychiatrie, 1882, vol. xvii. p. 63.
Mickle. British Medical Journal, 1881.
Nachther. Deutsche medicinische Wochenschrift, 1886, p. 515 (case resembling opium poisoning).
Numley. Transactions of the Pathological Society of London, 1890, vol. xi.
Peabody. Medical Record, 1882.
Querolo. Review in Revue Neurologique, 1900, vol. viii. p. 470.
Raymond, F. Präger medicinische Wochenschrift, 1886, vol. xxxiv., No. 13.
Rovie. Journal of Mental Science, July, 1880.
Russell and Taylor. Brain, spring number, 1890 (multiple hemorrhage).
Schultz. Präger medicinische Wochenschrift, 1881, No. 37.
Schultz, Fr. Deutsche Zeitschrift f. Nervenheilkunde, 1895, vol. viii. p. 1 (case occurring in newborn).
Senator. Charité-Annalen, 1891, vol. xvi. p. 299.
Spitzka. Journal of Neurology and Psychiatry, 1883.
Thomas. Lancet, 1878, vol. ii. p. 618 (case like opium poisoning).
Vrain. Präger medicinische Vierteljahresschrift, 1887 (multiple hemorrhages).
Wadsworth and Spiller. Journal of the American Medical Association, 1900, p. 1070.
Wallace. Lancet, April 5, 1890.
Willcocks. British Medical Journal, 1881.
Wilks. Diseases of Nervous System, 1883, p. 104.

Softenings.

Achard and Levi. Gazette Hebdomadaire, 1901, p. 704.
Babinsky. Iconographie de la Salpêtrière, 1902.
Ballisari. Annales de Neurologie, 1898, vol. xvi.
Bleuler. Deutsche Archiv f. klin. Medicin, vol. xxxvii. p. 527.
Bonnus. Revue Neurologique, 1897, vol. vi. p. 88.
Brasch. Neurologische Centralblatt, 1883, vol. ii. p. 226.
Darolles. Charité-Annalen, 1877, vol. ii. (cited by Oppenheim).
Dumenil. Arch. gén., April, 1875.

Eichorst. Charité-Annalen, 1876, vol. i.
Gardner, W. E. Glasgow Medical Journal, 1899.
Goldscheider. Charité-Annalen, 1891, vol. xvi. p. 162.
Giuffrè. Revista Clinica and Neurologische Centralblatt, 1896.
Gottstein. Biermer's Lehrbuch de Kehlkopf.
Hallopeau. Archives de Physiologie, 1876, p. 794.
Homen. Virchow's Archiv, 1882, vol lxxxviii. p. 61.
Hun. New York Medical Journal, April, 1887.
Kahler. Präger medicinische Wochenschrift and Charité-Annalen, 1885, vol. xii.
Ladame and von Monokow. Iconographie de la Salpêtrière, 1900.
Leclerc. Lyon Médical, 1901, vol. xcvii. p. 533.
Leyden. Archiv f. Psychiatrie, 1876, vol. vii. (two cases).
Makowski. Archiv f. Psychiatrie, 1892, vol. xxiii. p. 367.
Maleieff. Revue Neurologique, cited, 1901, p. 305.
Mills. International Clinics, 1895, vol. iii. p. 150.
Moeli. Archiv f. Psychiatrie, vol. xxiv. p. 655.
Oppenheim and Siemerling. Neurologische Centralblatt, 1885, p. 461.
Prout. Archiv f. klin. Medicin, 1872, vol. viii. p. 606.
Ransohoff. Archiv f. Psychiatrie, 1894, vol. v.
Ransohoff. Deutsche Zeitschrift f. Nervenheilkunde, 1899, vol. xv.
Reinhold. Deutsche Zeitschrift f. Nervenheilkunde, 1894, vol. v.
Senator. Charité-Annalen, 1885, vol. xvi.
Senator. Archiv f. Psychiatrie, 1883, vol. xiv. p. 643.
Taylor, H. British Medical Journal, 1871, No. 4.
Volland. Archiv f. Psychiatrie, 1899, vol. xxxii. p. 705.
Van Oordt. Deutsche Zeitschrift f. die Nervenheilkunde, 1896, vol. viii. p. 183.
Vulpian. Review in Centralblatt f. die medicinische Wissenschaften, 1886.
Wallenburg. Deutsche Zeitschrift f. Nervenheilkunde, 1897, vol. ii.
Wallenburg. Archiv f. Psychiatrie, 1897, vol. xxxiv.
Willigk. Präger Vierteljahresschrift, 1875, No. 126.

ACUTE LYMPHOCYTIC LEUKEMIA, WITH REFERENCE TO ITS MYELOGENOUS ORIGIN.

By A. O. J. KELLY, A.M., M.D.,
OF PHILADELPHIA.

During the last few years the blood, the lymph glands, and the bone-marrow have been the subject of considerable study by clinicians and pathologists, and, although the literature has been enriched by a number of valuable contributions, much remains to be learned. Especial interest has centered in leukemia and leukemic-like diseases, particularly acute lymphocytic (or lymphatic) leukemia. This, although by no means as rare as formerly supposed, is nevertheless sufficiently uncommon to merit continued study and the report of additional cases; and warrant for both the study and the report is found in our lack of knowledge of the etiology and histogenesis of the disease, in the differences of opinion regarding the nature and the interrelationship of the different varieties of leukemia, and in the recent reports of cases of lymphocytic-myelocytic (lymphatic-myelogenous, transitional, mixed, or intermediate) leukemia, and of leukemia apparently developing out of pseudoleukemia.

This study was suggested by the subjoined four cases that came under observation at the German Hospital, of Philadelphia, within a comparatively brief period. For the privilege of studying the patients while in the hospital and of reproducing here the clinical histories, I am very much indebted to Dr. James C. Wilson, Physician-in-Chief, and Dr. John B. Deaver, Surgeon-in-Chief, to the German Hospital.

Case I.—*Male, aged forty-nine years. Under observation two months; duration of symptoms ten weeks. Initial symptom, sore throat (tonsillitis); later, irregular fever, chills, pain, tenderness, and enlargement of the liver. First count of the leukocytes,* 17,000; *later,* 35,000, 105,400, *and* 119,500. *Lymphocytes,* 98.3 *per cent. No enlargement of the lymph glands clinically. At the necropsy moderate enlargement of the mesenteric and retroperitoneal glands, slight enlargement of the spleen, lymphocytic infiltration of the organs, and lymphadenoid bone-marrow.*

Stephen G., a white male, aged forty-nine years, a native of Germany, and a mill-hand by occupation, was first seen in private practice by my father on August 17, 1900, suffering from what appeared to be an attack of acute tonsillitis. The patient's father died of asthma, his mother of pneumonia, and five brothers and two sisters in infancy of causes not ascertainable. One sister is living and well. The patient's wife had six children, five of whom are living and well; one died of diarrhea. He does not remember having had any of the diseases of childhood. He had malaria at the age of thirty-five years, and he had frequent attacks of pains in his joints. He uses tobacco and alcohol moderately. He denies venereal infection. He had always considered himself in good health until the beginning of August, 1900, when he began to feel out-of-sorts without any very definite complaint. His appetite failed him, he felt disinclined to exertion, and became readily tired. Finally he developed what appeared to be acute tonsillitis. On examination the tonsils were much swollen, almost meeting in the median line, and there was a small ulcer on the roof of the mouth (that never healed). At this time examination of the leukocytes by Dr. M. Howard Fussell revealed 17,000 to the cubic millimeter. Soon the patient became dyspneic, and developed irregular chills and fever, and the region of the liver became tender. On examination the liver was found to be enlarged. Another count of the leukocytes by Dr. Fussell revealed 35,000.[1] This, together with the enlarged and tender liver and the irregular chills and fever, suggested to a surgeon whom the patient consulted a diagnosis of abscess of the liver, for which he proposed operation. The patient, however, was induced to go to the German Hospital, where he was admitted October 9, 1900, to the service of Dr. Wilson. By this time he had lost thirty pounds in weight; he was dyspneic, weak, prostrated, and pale, and he complained of spells of severe pain in the region of the liver. On admission his temperature was 102.2° F., and during the four days that he remained in the hospital it ranged between 100.8° and 103° F., his pulse between 100 and 120, and his respirations between 26 and 34. The skin had a slightly yellow tinge, but there was no jaundice. The tongue was coated, the teeth poor, the tonsils enlarged, and the breath very foul. The lungs appeared to be normal on examination. There was a systolic murmur in the region of the apex of the heart and a roughened aortic sound. There was no enlargement of the superficial lymph glands. The spleen was slightly enlarged to percussion, reaching almost to the free margin of the ribs, but it was not tender. Liver slightly enlarged and tender. On October 10 the urine was acid in reaction, had a specific gravity of 1008, contained a slight amount of albumin, and granular and hyaline casts. Examination of the blood revealed:

Hemoglobin	17 per ct.
Erythrocytes	1,050,000
Leukocytes	105,400
Ratio of leukocytes to erythrocytes	1 to 10

[1] The two counts of the leukocytes by Dr. Fussell are given from memory, the record unfortunately having been mislaid.

On October 11 the absence of enlargement of the superficial lymph glands was again noted. Examination of the blood revealed:

Hemoglobin	14 per ct.
Erythrocytes	1,270,000
Leukocytes	119,500
Ratio of leukocytes to erythrocytes	1 to 11.5
Lymphocytes (98.3 per cent.; large 84.2, small 14.1)	117,469
Polynuclear neutrophiles (0.4 per cent.)	478
Neutrophilic myelocytes (0.9 per cent.)	1,075
Basophiles (0.4 per cent.)	478

In view of the manifestly bad prognosis the patient, of his own volition, returned home October 12, where he died October 17. Another examination of his blood, made October 13, revealed:

Leukocytes	163,000
Lymphocytes (96 per cent.; large 90, small 6)	156,480
Polynuclear neutrophiles (0.6 per cent.)	978
Eosinophiles (0.2 per cent.)	326
Neutrophilic myelocytes (3 per cent.)	4,890
Basophiles (0.2 per cent.)	326

The following are the notes of the necropsy made by myself, at the patient's house, October 17, 1900, ten hours after death:

The body is that of a well-developed male subject, with good bony development, moderate panniculus adiposus, and flabby musculature. The nutrition is poor and the skin pale. There is moderate postmortem rigidity and slight postmortem lividity in the dependent portions of the body. The preperitoneal adipose tissue is moderate in amount. The abdominal and thoracic muscles are pale. The lymph glands of the neck are not enlarged. The marrow of the sternum and the ribs is red in color, but presents no gross deviations from the normal. The left pleura is glistening, transparent, pale, non-adherent, and contains no fluid. The left lung is normal in size, pale, mottled grayish-black in color, normal in consistency, crepitant throughout, and reveals slight hypostatic congestion. The section surface is smooth, moist, glistening, pale pinkish in color, and exudes a small amount of frothy serum and blood. The lung is firm and tenacious, and contains no tubercle. The bronchi are normal in caliber, contain a slight amount of mucus; their mucous membrane is pale. The right pleura and right lung present appearances analogous to their fellows. The peribronchial lymph glands are anthracotic, but not enlarged. The pericardium is normal in extent, non-adherent, and contains 10 c.c. of clear, straw-colored fluid. The heart is contracted and normal in shape, position, and size. The epicardium is glistening, transparent, and pale, and contains a normal amount of fat. The cavities of the heart are about normal in capacity and contain a slight amount of yellowish, clotted blood. The orifices of the heart are normal in size. The mitral, aortic, tricuspid, and pulmonary valve leaflets are normal and competent. The left ventricle is slightly increased in thickness. The heart muscle is pale and somewhat friable; the coronary vessels and the aorta are normal. The peritoneum is glistening, transparent, pale, non-adherent, and

contains no fluid. The liver is about one-fourth larger than normally, but is normal in shape and elasticity. The surface is smooth, the edges fairly sharp, the capsule smooth and transparent. The section surface is glistening, moist, smooth, pale reddish-brown in color, and exudes a slight amount of blood. The liver lobules are moderately distinct; the gall-bladder is normal in size and contains fluid bile. The regional lymph glands are not enlarged. The spleen is about one-third larger than normally; it is normal in shape and moderately firm in consistency; its capsule is normal. The section surface is dark reddish-brown in color, smooth and firm, and presents no noteworthy deviations from the normal. The right kidney is about one-half larger than normally. Its capsule strips readily, leaving a smooth, firm, pale, and somewhat yellowish surface. The section surface is glistening and pale in color. The cortex is slightly increased in thickness. The left kidney presents similar appearances. Both ureters and both adrenals are normal. The bladder contains a small amount of clear urine and is normal in appearances. The stomach is normal in position and size, and contains some turbid fluid; its mucous membrane is pale; the duodenum is normal; the pancreas is pale. The mesentery is fatty and contains a large number of moderately enlarged lymph glands. A portion of the ileum excised reveals a large, infiltrated, ulcerated and necrotic Peyer's patch, in many respects resembling a typhoid ulcer. The retroperitoneal lymph glands are moderately enlarged. The brain and spinal cord were not examined.

Case II.—*French, aged forty-five years. Under observation six days; duration of symptoms, four and a half weeks. First symptoms developed eighteen days after the fourth parturition, and, consisting of chills, fever, sweats, and persistent metrorrhagia, suggested postpuerperal sepsis; later, epistaxis and melena and subcutaneous hemorrhages. First count of the leukocytes,* 203,200; *later,* 241,200, 302,400, 514,400, 406,000, 268,400, *and* 567,200. *Leukocytosis* 37 *per cent. No enlargement of the lymph glands clinically. At the necropsy slight enlargement of the lymph glands and the spleen, lymphocytic infiltration of the organs, and lymphadenoid bone-marrow.*

Mary H., a white married woman, aged forty-five years, a native of Germany and a housewife by occupation, was admitted to the German Hospital, to the service of Dr. Deaver, March 31, 1902, with the diagnosis of postpuerperal sepsis. Her father died at the age of sixty-six years, of "blood poisoning," and her mother at the age of sixty-five years, of general weakness. Four brothers and three sisters are living and well; seven brothers and sisters are dead, of causes not ascertainable. The patient had typhoid fever when twelve years of age. She has had four children and three miscarriages. She was well until after the birth of her fourth child, six weeks prior to admission to the hospital. The labor and the puerperium appeared to be normal, and the patient was able to be up and about ten days after the birth of the child. On the eighteenth day, however, she had a chill, accompanied by a shaking sensation, fever, and sweat. The lochia persisted and she experienced some pain in the lower part of the abdomen. During the

twenty-four hours preceding admission to the hospital her nose had bled continuously.

On admission the patient was weak, pale, flabby, and somewhat delirious. There was hemorrhage from the right nostril, and the abdomen was slightly distended, tender, and painful about the umbilicus. The tongue was coated and dry, the breath foul, and herpes were on the lips. The nostril was cleansed and stimulants were administered. Later a 4 per cent. solution of adrenal extract was used in the nostril to control the epistaxis. Vaginal examination revealed a soft cervix, subinvolution of the uterus, and a foul, bloody discharge. The spleen was found to be enlarged, but no enlargement of the lymph glands could be made out. On admission the patient's temperature was 103° F., and her pulse 88. The following morning the temperature was 101.2° F., and the pulse 120. The urine was acid in reaction, had a specific gravity of 1017, contained a small amount of albumin and epithelial cells and leukocytes. Examination of the blood April 1 revealed:

Hemoglobin	45 per ct.
Erythrocytes	2,800,000
Leukocytes	208,650
Ratio of leukocytes to erythrocytes	1 to 13.5
Lymphocytes (92.4 per cent.; large 90, small 2.4)	192,746
Polynuclear neutrophiles (1.5 per cent.)	3,129
Eosinophiles (0.1 per cent.)	209
Basophiles (6 per cent.)	12,516

In consequence of the results of the examination of the blood, the patient was transferred to the medical wards, to the service of Dr. Wilson. She was still delirious, very weak, and markedly dyspneic. Examination of the nose by Dr. Bliss revealed a large area of ulceration in the right nostril. Bleeding continued from the nose and the mouth, and later blood was observed in the stools and the urine. The spleen was still slightly enlarged. Examination of the blood April 2 revealed:

Leukocytes	243,000

Examination of the blood April 3 revealed:

Leukocytes	332,400
Lymphocytes (95.6 per cent.; large 90, small 5.6)	317,775
Polynuclear neutrophiles (2.2 per cent.)	7,313
Eosinophiles (0.1 per cent.)	332
Basophiles (2.1 per cent.)	6,980

On April 4, in addition to the albumin, casts were found in the urine. The patient's temperature had continued to range between 99.2° F. and 102.2° F., and her pulse between 104 and 180. Examination of the blood revealed:

Hemoglobin	20 per ct.
Erythrocytes	1,390,000
Leukocytes	314,300
Ratio of leukocytes to erythrocytes	1 to 4.4

Gradually the patient became more prostrated and comatose, [illegible] and subcutaneous hemorrhages developed, the malodorous vaginal discharge continued, and, despite active treatment with saline infusion, stimulants, etc., the patient died at 6.25 P.M., April 5, 1903. Examination of her blood on the morning of her death, before and after saline transfusion, revealed

	10.30 A.M., before transfusion.	11 A.M., after transfusion.
Leukocytes	406,000	268,000
Lymphocytes (94.7 per cent.)	384,482	255,980 (95 per ct.)
Polynuclear neutrophiles (2.3 per ct.)	9,333	6,442 (2.4 ")
Eosinophiles (1 per cent.)	4,060	2,147 (0.8 ")
Basophiles (2 per cent.)	8,120	4,831 (1.8 ")
Coagulation time		170 seconds.

Examination of her blood at 5 P.M. on the day of her death revealed

Hemoglobin	10 per ct.
Erythrocytes	1,380,000
Leukocytes	567,200
Ratio of leukocytes to erythrocytes	1 to 2.4
Lymphocytes (97.2 per cent.)	551,318
Polynuclear neutrophiles (1.2 per cent.)	6,806
Eosinophiles (0.6 per cent.)	3,403
Basophiles (1 per cent.)	5,671

The following are the notes of the necropsy (No. 458) made by myself April 6, 1902, sixteen hours after death:

The body is that of a well-developed female subject, with good bony development, good musculature, and considerable panniculus adiposus. The nutrition is good. There is a moderate postmortem rigidity and postmortem lividity in the dependent portions of the body. On the left arm there is a small incised wound, evidently the result of transfusion. On the fingers there are a number of small hemorrhagic foci, evidently the consequence of punctures for examining the blood. In addition there are about a dozen hemorrhagic areas, varying in size from 1 mm. to 3 mm. in diameter on the arms, trunk, and legs; otherwise the skin is pale. There is slight edema of the legs. The preperitoneal adipose tissue is considerable in amount. The left pleura is glistening, transparent, pale, non-adherent, and contains no fluid. The left lung weighs 400 grams, is pale, mottled grayish-dark in color, and firm in consistency. It is crepitant throughout and shows slight hypostatic congestion. The section surface is smooth, moist, glistening pale grayish in color, and crepitant throughout. It exudes a frothy serum and a slight amount of blood. The lung contains no tubercles and no cavities. The bronchi are normal in size and appearance, and contain a slight amount of mucus. The right pleura is dull, cloudy, pale, thickened and universally adherent by firm, fibrous adhesions. The right lung weighs [illegible] grams and presents appearances similar to its fellow, except that at the base of the upper lobe there is an area 6 cm. in diameter, increased in consistency, dark reddish-brown in color, and much diminished in air contents. The peribronchial lymph glands are slightly enlarged and anthracosic. The peri-

cardium is normal in extent, non-adherent, and contains no fluid. The heart is dilated, normal in shape and position, and weighs 320 grams. The epicardium is glistening, transparent, and pale. The subepicardial adipose tissue is normal in amount. The left auricle and ventricle contain a moderate amount and the right auricle and ventricle a considerable amount of pale, reddish, clotted blood. The left auricle and ventricle appear normal in capacity. The right side of the heart is somewhat dilated. The mitral, aortic, tricuspid, and pulmonary valve leaflets are normal and competent. The left ventricle is 8 mm. to 12 mm. in thickness, the left auricle 2 mm. to 5 mm., the right ventricle 5 mm. to 6 mm., and the right auricle 1 mm. to 3 mm. The heart muscle is pale reddish in color and firm in consistency. The coronary vessels and the aorta are normal. The omentum is normal in size, apron-like in shape, and fatty. The peritoneum is glistening, transparent, pale, non-adherent, and contains no fluid. The liver is 28 cm. in length, 24 cm. in breadth, and 8.5 cm. in thickness. It weighs 2200 grams, is normal in shape and elasticity, and firm in consistency. Its surface is smooth, its edges sharp, and its capsule normal. The section surface is glistening, moist, smooth, pale yellowish-brown in color, and exudes a slight amount of blood. The liver lobules are moderately distinct. The gall-bladder is slightly increased in size, and contains a calculus measuring 5 x 5.5 x 3.5 cm. The cystic, hepatic, and common bile ducts are patulous. The regional lymph glands are normal in size and appearance. The spleen measures 17.5 x 11 x 4 cm. It weighs 400 grams, is normal in shape, firm in consistency, and its capsule is normal. The section surface is dark reddish-brown in color, slightly granular, and moderately firm. The pulp and trabeculæ appear normal; the follicles are distinct. The right kidney measures 13 x 6.5 x 3 cm., and weighs 200 grams. Its capsule strips readily, leaving a smooth, pale surface. The section surface is glistening and pale reddish in color. The cortex measures 8 mm. in thickness. The pelvis reveals extensive hemorrhage into the mucous membrane. The left kidney measures 15 x 5.5 x 3.3 cm., and presents appearances similar to its fellow, including the extensive hemorrhage into the mucous membrane of the pelvis. Both ureters and both adrenals are normal. The bladder contains a slight amount of urine; its mucous membrane is pale. The stomach is normal in position and size, and contains some turbid fluid. Its mucous membrane is congested, but otherwise it is normal. The mucous membrane of the duodenum is congested and reveals several hemorrhagic foci. The pancreas measures 22 x 3 x 2.5 cm., and weighs 130 grams. It is pale in color and firm in consistency. Its ducts are normal. The ileum, cecum, and colon, especially the ileum, reveal some hemorrhagic foci in the mucous membrane. The retroperitoneal glands are slightly enlarged. The marrow of the right femur is quite red in color, in some places firm, but in others soft.

CASE III.—*Male, aged eleven years. Under observation twenty-four days; duration of symptoms, almost three months. Initial symptoms, swelling of the glands of the neck; later, considerable enlargement of all of the glands of the*

bed, irregular fever, and submucous and subcutaneous hemorrhages. First count of the leukocytes, 378,000; later, 198,000. Lymphocytes, 98.6 per cent. At the necropsy marked enlargement of all the lymph glands of the body, slight enlargement of the spleen, marked enlargement of the thymus, and lymphocytic infiltration of the organs.

Edward H., a white male, aged eleven years, a native of the United States, was admitted to the Mary J. Drexel Home July 24, 1902, and the following history elicited: His father died of Bright's disease. His mother and three younger brothers and sisters are living and well. One sister died of pulmonary tuberculosis, aged seventeen years. Aside from measles, pertussis, and chicken-pox, which he had in early childhood, the patient was well until two months prior to admission to the Home, when he fell, striking the back of his head. Following this he vomited considerably. One week later a swelling was noticed back of his right ear. A week later this became painful, and gradually increased in size and extent, spreading down the neck and around to the other side. A week before admission his jaw began to get stiff, his gums to bleed, and he became quite weak. On admission he was very weak and much prostrated. His jaw hung down and had to be supported when he was eating or drinking. The bleeding from the gums was quite marked. The faucial tonsils were much enlarged, almost occluding the pharyngeal space and necessitating breathing through the mouth. The cervical, axillary, epitrochlear, and inguinal glands were enlarged considerably. The spleen was somewhat enlarged, reaching to about the margin of the ribs. The liver appeared to be slightly enlarged. Examination of the blood July 24 revealed:

Hemoglobin	65 per ct.
Erythrocytes	3,590,000
Leukocytes	378,000
Ratio of leukocytes to erythrocytes	1 to 9.5
Lymphocytes (98.6 per cent.; large 97, small 1.6)	371,708
Polynuclear neutrophiles (1 per cent.)	3,780
Eosinophiles (0.4 per cent.)	1,512

Examination of the blood July 30 revealed:

Leukocytes	198,000
Lymphocytes (97 per cent.; large 96 5, small 0.5)	192,060
Polynuclear neutrophiles (2 per cent.)	3,960
Eosinophiles (0.5 per cent.)	990
Basophiles (0.5 per cent.)	990

The urine on several occasions was acid in reaction, had a specific gravity varying between 1011 and 1014, contained a small amount of albumin, and a considerable amount of blood. During his stay in the Home the patient's temperature was continuously above normal, fluctuating between 98.7° and 104° F. Shortly before death it reached 102.2° F. His pulse varied between 96 and 144, being usually above 120. Gradually the patient became weaker, the swelling and hemorrhagic suffusion of the mucous membrane of the mouth and nose became more marked, and subcutaneous hemorrhages became

more numerous. The swelling of the lymphatic glands persisted. Under progressive asthenia the patient died August 17, 1902, at 10 P.M.

The following are the notes of the necropsy (No. 490) made by myself August 18, 1902, twelve hours after death:

The body is that of a fairly well-developed male subject, with good bony development, fair musculature, and moderate panniculus adiposus. The general nutrition is fair, the skin pale, aside from a few subcutaneous punctiform hemorrhages on the legs and arms. The glands of the neck, groins, and axillæ show through the skin as very much enlarged, ovoid masses, fairly firm to the touch. The glands of the neck especially are much enlarged. The preperitoneal adipose tissue is moderate in amount. The abdominal and thoracic muscles are pale. The papillæ of the tongue are much enlarged. Both tonsils are much swollen, enlarged, moderately firm, and the surface slightly ulcerated. The pharyngeal mucous membrane shows increase of the lymphoid tissue. The lymphatic glands of the neck are very much enlarged, moderately firm, and pinkish in color. The salivary glands appear normal. Upon removing the sternum, at the normal situation of the thymus gland, intimately adherent to the pericardium, is a pinkish, firm, glistening mass (evidently the enlarged thymus), 5 x 8 x 1 cm. to 2 cm. On section it is fairly firm, pinkish in color, and glistening. The left pleura is glistening, transparent, pale, non-adherent, and contains no fluid. The left lung weighs 280 grams, is pale, mottled grayish-black in color, firm in consistency, crepitant throughout, and reveals slight hypostatic congestion. The section surface is smooth, moist, glistening, pale, grayish-red in color, exudes a moderate amount of blood and frothy serum, and reveals no tubercles and no cavities. The bronchi are normal in appearance and contain a small amount of mucus. The right lung weighs 300 grams. In general the right pleura and lung reveal appearances analogous to their fellows. The bronchial glands are moderately enlarged, anthracotic, and reveal caseous and calcareous areas. The pulmonary vessels are normal. The pericardium is normal in size and appearance and contains 15 c.c. of clear amber fluid. The heart is dilated, normal in position and shape, and weighs 125 grams. The epicardium is glistening, transparent, pale, and reveals many punctiform hemorrhages. The subepicardial adipose tissue is normal in amount. The cavities of the heart, which are apparently normal in capacity, contain a moderate amount of mixed colored clots. All of the valve leaflets are normal. The left ventricle measures 6 mm. to 10 mm., the left auricle 2 mm. to 3 mm., the right ventricle 3 mm. to 5 mm., and the right auricle 1 mm. to 3 mm. The heart muscle is pale in color and firm in consistency. The coronary vessels and the aorta appear normal. The omentum is moderate in size and fatty; it contains many roundish nodules, moderately firm in consistency, pinkish in color, and about the size of a split pea. The peritoneum is glistening, transparent, pale, non-adherent, and contains no fluid. The liver measures 20 x 18 x 9 cm., is normal in shape, firm in consistency, and weighs 1600 grams. Its surface is smooth, its edges

roundish, and the capsule normal. The section surface is smooth, moist, pale yellowish, and contains a slight amount of blood. The liver lobules are not especially distinct. The gall-bladder is normal, contains fluid bile; the cystic, hepatic, and common bile ducts are patulous. The regional lymph glands are much enlarged. The spleen measures 16 x 10 x 4.5 cm., weighs 300 grams, is normal in shape, and moderately firm in consistency. The section surface is dark reddish-brown in color, slightly granular, and moderately firm. The pulp seems to be increased, the follicles are distinct, and the trabeculæ slightly increased. The right kidney measures 11 x 5.5 x 2.5 cm., is normal in shape, and weighs 150 grams. Its section surface is smooth, pale pinkish in color, and moderately firm in consistency. The cortex is 5 mm. to 6 mm. in thickness. The mucous membrane of the pelvis is markedly hemorrhagic. The left kidney measures 12 x 5.5 x 3 cm., and weighs 150 grams. It presents appearances analogous to its fellow, including the markedly hemorrhagic condition of the pelvis. Both ureters and adrenals are normal. The bladder contains a small amount of urine, and the mucous membrane reveals a large number of hemorrhagic foci. The stomach is normal in size and position; its mucous membrane is pale, but otherwise normal. The duodenum is normal. The jejunum, ileum, cecum, and colon reveal considerable thickening of the lymphoid follicles, and the ileum in addition reveals slight ulceration of the follicles and of Peyer's patches. The pancreas is normal in size, pale in color, and firm in consistency. The mesentery contains many very large lymphatic glands, which are moderately firm in consistency and pinkish in color. The retroperitoneal lymph glands are very much enlarged, moderately firm, and pinkish in color. The brain and spinal cord were not examined.

Case IV.—*Male, aged forty-eight years. Under observation seven weeks; duration of symptoms indefinite (the patient having been in rather poor health for several months, but, as he thought, ill enough for treatment for only seven weeks). Initial symptoms, general weakness, and upon examination slight enlargement of the lymph glands; later, marked swelling of the cervical lymph glands, irregular fever, dyspnea, submucous and subcutaneous hemorrhages. First count of the leukocytes,* 9000; *later,* 6000, 5200, 18,200, *and* 37,000. *Lymphocytes,* 98 *per cent. At the necropsy marked enlargement of the lymph glands, except the inguinal and the axillary; enlargement of the spleen; gumma and syphilitic cirrhosis of the liver; lymphadenoid bone-marrow.*

William L. S., a white male, aged forty-eight years, a native of the United States and a factory foreman by occupation, presented himself at the medical out-patient department of the German Hospital August 5, 1902, complaining of general weakness. His father and two sisters are living and well. His mother died at the age of forty-two years, presumably of a liver disorder. The patient had measles, chicken-pox, and pertussis in childhood, malarial fever from his eighteenth to his twenty-fifth year, and syphilis at his thirty-sixth year. He states that he had a chancre, but no secondaries, and that he was under treatment for a year. He had specific urethritis six times and

some stomach disorder, followed by jaundice, at the age of forty-three years. He indulges in alcohol to excess and smokes considerably. In March, 1902, he fell twenty-five feet to a pile of steel, landing on his right heel. Soon thereafter both legs began to swell. The right became the worst, varicose veins developed, and an ulcer resulted, which was treated at the surgical out-patient department of the German Hospital. He states that he has not been well since the fall. He has grown weak and has lost his appetite. He has had attacks of diarrhea, due to dietetic indiscretions, but no nausea and no vomiting. He has had occasional attacks of jaundice, with clay-colored stools. Recently he has been troubled with vertigo, and has developed slight swelling of the ankles and eyelids. Examination revealed slight jaundice, great enlargement of the spleen, moderate enlargement of the liver, especially of the left lobe; leukoderma of the hands, wrists, and abdomen, and a cicatrix from an old ulcer on the leg. Examination of the blood revealed:

Hemoglobin	60 per ct.
Erythrocytes	3,760,000
Leukocytes	9,000
Ratio of leukocytes to erythrocytes	1 to 418
Lymphocytes (small 4 per cent., large 94 per cent.)	8,820
Polynuclear neutrophiles (1.5 per cent.)	135
Eosinophiles (0.5 per cent.)	45

In consequence of the condition of the blood the patient was advised to enter the hospital, which he did August 13, 1902, being admitted to Dr. Wilson's service. At this time he was a fairly well-nourished man, with slight jaundice. The spleen was markedly enlarged, extending three and one-half inches below the costal margin; its edge could be felt and the notches made out. The left lobe of the liver was enlarged, extending halfway between the ribs and the umbilicus. The cervical, epitrochlear, and inguinal lymph glands were slightly enlarged and distinctly palpable. A soft systolic murmur was audible at the apex of the heart. The lungs were normal. The urine was pale yellow in color, faintly alkaline in reaction, had a specific gravity of 1012, contained a trace of albumin, but no sugar. Microscopically there were cylindroids, epithelial cells, and leukocytes. Examination of the blood August 13 revealed:

Hemoglobin	43 per ct.
Erythrocytes	2,750,000
Leukocytes	6,000
Ratio of erythrocytes to leukocytes	1 to 458.3
Lymphocytes (small 9 per cent, large 87.5 per cent.)	5,790
Polynuclear neutrophiles (0.5 per cent.)	30
Eosinophiles (1 per cent.)	60
Neutrophilic myelocytes (1 per cent.)	60
Eosinophilic myelocytes (1 per cent.)	60

Examination of the blood August 19 revealed:

Hemoglobin	55 per ct.
Erythrocytes	2,430,000
Leukocytes	5,200
Ratio of leukocytes to erythrocytes	1 to 467.3

On admission to the hospital the patient's temperature was normal, and it did not go above normal except once, the evening of August 18, when it reached 99.4° F. His pulse varied between 62 and 88, being usually from 72 to 76. His respirations varied between 14 and 22, being usually 18.

The patient was given Fowler's solution—five drops three times a day, and increasing one drop each three doses. On August 19, of his own volition, the patient left the hospital. He returned to have his blood examined on August 27, when the following was revealed:

Hemoglobin	44 per ct.
Erythrocytes	2,360,000
Leukocytes	18,200
Ratio of leukocytes to erythrocytes	1 to 129.2

He was readmitted to the surgical wards of the hospital, under the service of Dr. Deaver, September 5, 1902. At this time the right side of his face, the submaxillary region, and the right side of his neck were swollen. Fluctuation being detected at one point below the angle of the jaw, an incision was made and 5 c.c. of pus was evacuated. The patient subsequently began to lose flesh and strength; he became dyspneic, and small areas of hemorrhage developed in different parts of his body, especially about the head and neck. Examination of the blood September 8 revealed:

Hemoglobin	35 per ct.
Erythrocytes	2,190,000
Leukocytes	37,600
Ratio of leukocytes to erythrocytes	1 to 58.2
Lymphocytes (small 2 per cent., large 96 per cent.)	36,848
Polynuclear neutrophiles (1.5 per cent.)	564
Eosinophiles (0.5 per cent.)	188

On September 10 another abscess developed anteriorly to the first one. This being incised, a small amount of purulent matter was liberated. From this time on the patient gradually grew worse. His weakness became aggravated, his dyspnea marked, swallowing difficult on account of the swelling of the tissues of the neck and throat, and additional hemorrhages developed in different parts of the body. Albumin in traces continued in the urine. His temperature varied between 100° and 103° F., and his pulse between 84 and 100, from September 5 to 18; from September 19 to 21 his temperature fluctuated between 100° and 105° F., his pulse 100 to 148, and his respirations from 30 to 44. Finally the patient became unconscious, and died at 8.30 A.M., September 23, 1902.

The following are the notes of the necropsy (No. 503), made by myself, September 23, 1902, two and a half hours after death:

The body is that of a well-developed male subject, with good bony development, fair musculature, and moderate panniculus adiposus. There is moderate postmortem rigidity and postmortem lividity in the dependent portions of the body. The nutrition is fair. On the right side of the neck there is a small, granulating wound. The skin in general has a slight icteric hue. On the right tibia there is a pigmented scar, apparently the result of a healed

ulcer. The skin of the face, thorax, abdomen, hands, and arms is much pigmented, and shows intervening spots of leukoderma, which are now slightly icteric. The skin of the scalp, eyelids, and legs is the seat of many small hemorrhagic areas, about the size of a ten-cent piece. The eyelids are somewhat swollen on account of the hemorrhagic suffusions, and it is impossible to uncover the eyes. The abdominal and thoracic muscles are pale and reveal a number of small, hemorrhagic foci. All of the lymph glands of the neck are very much swollen and moderately firm. The left pleura is glistening, transparent, pale, non-adherent, and contains about 50 c.c. of serosanguinolent fluid. The left lung weighs 530 grams, is mottled grayish-black in color, firm in consistency, and reveals slight hypostatic congestion and normal air contents. The section surface is smooth, moist, glistening, pale in color, and crepitant throughout. It exudes a moderate amount of bloody and frothy fluid. The organ contains no tubercles and no cavities. The bronchi appear normal. The right pleura contains about 100 c.c. of serosanguinolent fluid. The right lung weighs 620 grams, and presents appearances similar to its fellow. The peribronchial lymph glands are very much enlarged, moderately firm, and very red in color. The pericardium is normal in extent, and contains about 10 c.c. of pale, clear, amber fluid. The heart is dilated, normal in position and shape, and weighs 320 grams. The epicardium in general is glistening, transparent, and pale; in addition it reveals, especially on its posterior aspect, as well as on its anterior, many punctate, hemorrhagic areas. The subepicardial adipose tissue is normal in amount. The cavities of the heart are about normal in capacity and contain a moderate amount of dark-red, clotted blood. The mitral, aortic, tricuspid, and pulmonary valve-leaflets are normal, and apparently all are competent. The left ventricle is 8 mm. to 12 mm. in thickness, the right ventricle 4 mm. to 7 mm., the left auricle 2 mm. to 4 mm., and the right auricle 1 mm. to 3 mm. The heart muscle is slightly pale and somewhat flaccid; the coronary vessels and the aorta are normal. A few fibrous adhesions bind the liver to the left flank; otherwise the peritoneum is glistening, transparent, and pale. The liver measures 25 cm. in length, 17 cm. in breadth, 9.5 cm. in thickness, and weighs 1750 grams. It is very much increased in consistency and somewhat distorted in shape; its surface is extremely granular and nodular, its edges sharp, and its capsule thickened, especially posteriorly along the suspensory ligament where the liver is adherent to the diaphragm. The surface reveals five or six deep stellate scars. The section surface is glistening, somewhat granular, pale in color, and exudes a small amount of blood. The liver lobules in general are fairly distinct. Radiating from the afore-mentioned scars bands of connective tissue pervade the organ, which is thus much indurated. In addition, in the left lobe of the organ and projecting somewhat from its surface, there is an irregular, fairly firm, whitish, or grayish-white, semitranslucent mass, about the size of a small fist. It is surrounded on all sides, and thus separated from the adjacent liver tissue, by thick, overgrown, fibrous connective tissue—evidently a gumma. The gall-bladder is distended

and contains fluid bile. The cystic, hepatic, and common bile ducts are patulous; the portal vein is normal. The regional lymph glands are much enlarged, moderately firm, and very red in color. The spleen measures 23 cm. in length, 17 cm. in width, 8.5 cm. in thickness, and weighs 1140 grams. The capsule is very much thickened, the outer surface being of cartilaginous consistency, 3 mm. to 4 mm. in thickness, and adherent to the surrounding tissues. On section the spleen is dark reddish-brown in color, slightly granular, and firm. The pulp is increased, the follicles rather distinct, and the trabeculæ increased. Adjacent to the spleen are four smaller structures, 4 x 3 x 4 cm. in size, resembling the spleen in general appearances, and evidently supernumerary spleens. The right kidney measures 13 cm. in length, 5.5 cm. in width, and 4.5 cm. in thickness. It is normal in shape and weighs 330 grams. The capsule strips readily, leaving a smooth, dark reddish-brown surface. The organ is somewhat softened, and the section surface glistening and dark reddish-brown in color. The cortex is from 7 mm. to 8 mm. in thickness. The pyramids are dark; the mucous membrane of the pelvis reveals many punctate hemorrhages. The left kidney measures 15 cm. in length, 7.5 cm. in width, 4 cm. in thickness, and weighs 320 grams. It presents appearances similar to its fellow. Both ureters are normal. Both adrenals are normal in size and shape, and somewhat softened and hemorrhagic. The bladder reveals a few hemorrhagic foci in the mucous membrane. The stomach is normal in position and shape, and contains some turbid fluid. Its mucous membrane and wall are normal, except at the pylorus, where there is much submucous thickening. The pancreas is normal in size and shape, pale in color, and firm in consistency. The large and small intestines reveal many small hemorrhages beneath the mucous membrane. The mesentery is normal aside from slight enlargement of the lymph glands. The retroperitoneal glands are very much enlarged, moderately firm, and very red in color. The inguinal glands are only slightly enlarged, quite firm, and white in color (in marked contrast to the previously mentioned very red glands). The axillary glands are not enlarged to palpation. The brain and spinal cord were not examined.

The following are the results of the microscopic examinations of the blood and organs in the different cases:

The Blood. The number of leukocytes varied considerably in the different cases—from a minimum of 6000 (Case IV.), of which 5790 (96.5 per cent., instead of the normal 22 to 25 per cent.) were lymphocytes, to a maximum of 567,200 (Case II.), of which 551,319 were lymphocytes. In the original and routine examinations of the blood, the figures of which are herewith reproduced, all of the non-granular mononuclear leukocytes were classed as lymphocytes.[1] A more careful study of the blood preparations, however,

[1] This is at least a matter of convenience; indeed, some writers frankly confess their inability to distinguish between the large lymphocyte and the so-called large mononuclear and transitional) leukocyte. This is due largely to the inherent limitations of Ehrlich's stain

renders it quite apparent that we can distinguish two varieties of non-granular mononuclear cells—the lymphocytes and the so-called large mononuclear leukocytes. Furthermore, of the lymphocytes, two varieties may be distinguished—the large and the small; that is, there are extremes of size and of nuclear and protoplasmic appearances that readily distinguish one cell from the other; but so many are the cells intermediate in size and appearances between the extremes that the distinction is often very largely a matter of the personality of the investigator. This may also be said to be at least partly true as regards the large lymphocytes and the so-called mononuclear leukocytes. A number of the cells, however, are clearly distinguishable as large mononuclear leukocytes, differing in size and in protoplasmic and nuclear appearances from the lymphocytes. In certain other cells, on the contrary, the distinctions are not always so clear, the difficulties being increased by the fact that many of the cells are degenerated and that many of the mononuclear leukocytes appear as free nuclei, the consequence, evidently, of technical procedures. The majority of the white blood cells, however, are large lymphocytes, the percentages varying in the different cases from a minimum of 84.2 in Case I. to a maximum of 97 in Case II. It is noteworthy and in conformity with the blood condition in most of the reported cases that approximately 95 per cent. of the white cells in all of the cases, with the exception of Case I., are large lymphocytes. The lymphocytes vary in size—from 7μ to 13μ. They present the ordinary appearances of lymphocytes—that is, those that can be differentiated as small lymphocytes consist of a relatively large, roundish, concentrically placed, and rather deeply staining nucleus, surrounded by a narrow rim of non-granular protoplasm that is distinctly basophilic with eosin and methylene blue mixtures, but a pale greenish, rather indefinite color with Ehrlich's triple stain. The nuclei of the large lymphocytes are larger than those of the small lymphocytes; they are often eccentrically placed, sometimes slightly indented, and show less affinity for the stain; but otherwise the two types of cell are much alike in appearance. As already mentioned, it is impossible to apportion some of the cells; one can only say that they are lymphocytes. The basophilia of the protoplasm, however, is especially conspicuous in some of the large lymphocytes. The non-granular mononuclear cells occur in varying proportion in the different cases. As already intimated, it is difficult to determine the exact number of these cells in the different cases; some are markedly degenerated, some appear as free nuclei, and of some it is difficult to say whether they are lymphocytes or large mononuclear leukocytes. They are present, however, in all of the

which, nevertheless, has been the means of our learning so much. While we feel that we are tolerably well informed concerning the granular cells (granulocytes), our knowledge of the non-granular leukocytes is very imperfect, and we are certain of comparatively little relating to the development of the blood corpuscles. With some of the newer mixtures of methylene blue and eosin, however, we are enabled to study certain elements in the blood and blood-forming organs that previously were scarcely susceptible of differentiation.

cases, constituting certainly 6 per cent. of the white cells in Case I., 10 per cent in Case III , and from 6 to 10 per cent. in Cases II. and IV. They vary in size, being, as a rule, about 15μ in diameter, though the extremes of size are about 12μ and 18μ. The nuclei, situated sometimes concentrically, sometimes eccentrically, are large, filling about one-half of the cell, although relatively small as compared with the protoplasm. The cells contain considerably more protoplasm than do the lymphocytes, the increase in size of some of the cells being very largely a matter of protoplasm. The protoplasm is very faintly basophilic, staining very faintly, even fainter than the very pale nucleus. In some cases the protoplasm is scarcely, if at all, discernible, whereas some of the cells appear as free nuclei. Basophiles are present in Cases I., II., and III., varying in number from a minimum of 326 (0.2 per cent.) in Case I. to a maximum of 12,516 (6 per cent.) in Case II. The cells are mononuclear, and average about 10μ to 11μ in diameter. Many of the granular cells are metachromatic. There is nothing noteworthy about the few eosinophiles and polynuclear neutrophiles observed in the different cases. Some interest, however, attaches to the myelocytes found in Case I. (0.9 per cent.; 1075 to the c.mm.) and Case IV. (2 per cent.; 120 to the c.mm.). For the most part they present the ordinary features of neutrophilic myelocytes. Some of them, however, have at least metachromatic granules, while others appear to have both basophilic and neutrophilic granules, suggesting a genetic relationship between certain lymphocytes and certain myelocytes. Degenerative changes in the lymphocytes are observable in all the cases, but especially in Cases III. and IV. The degenerative changes consist of (1) budding—that is, extravasation or protrusion of small tufts of protoplasm along the edges of the cells, especially conspicuous in Case III. after saline transfusion; (2) vacuolation, present in all the cases, but especially marked in Cases II. and IV.; (3) hyaline transformation of the cellular protoplasm, in consequence of which it presents an affinity for acid stains, seen especially in Cases I. and IV.; (4) rupture and disappearance of the cellular protoplasm, seen in all the cases; and (5) slight karyorrhexis and more marked karyolysis, seen in all the cases, but especially marked in Case III. The only noteworthy changes in the erythrocytes are the oligocythemia, already indicated; slight poikilocytosis present in all the cases, but somewhat more marked in Cases I., III., and IV.; polychromatophilia in Cases II. and III., and a few nucleated red corpuscles (normoblasts) in Case III.

Lymph Glands. The lymph glands vary somewhat in appearance in the different cases. As already mentioned, Case I. revealed only moderate enlargement of the mesenteric and retroperitoneal glands; Case II., slight enlargement of the lymph glands in general; Case III , enlargement of all the lymph glands; and Case IV., slight enlargement of the inguinal and axillary glands, in marked contrast to the greatly enlarged cervical, thoracic, mesenteric, and retroperitoneal glands. Macroscopically the glands that were enlarged were somewhat softer and redder than normally; a few even

seemed hemorrhagic. In sections the glands that were only slightly enlarged show moderate deviation from the normal. In some of the glands the germ centers can be distinguished from the sinuses, although the distinctions are not as sharp as normally. This appears to be due largely to a great accumulation of cells in the sinuses, although the germ centers themselves appear to have expanded. In the greatly enlarged glands of Cases III. and IV. distinctions between the germ centers and the sinuses are almost completely, if not completely, effaced. Here and there one may imagine a sinus, but the general structure of the glands is quite homogeneous. The large majority of the cells infiltrating the glands are the large lymphocyte, a cell identical with that so abundant in the blood. It can be readily distinguished by its rather pale nucleus and basophilic protoplasm. In general it is well preserved, although degenerative changes, both karyolysis and karyorrhexis are to be seen. Readily distinguishable from the large lymphocyte is a small lymphocyte, with darkly staining nucleus and less protoplasm, apparently the ordinary or resident lymphocyte of the glands. This is much less numerous than the large lymphocyte, especially in the greatly enlarged glands. It is relatively more common in the slightly enlarged glands and in those almost if not quite normal in size, and it seems also to be more numerous in Case I. than in the other cases. Now and then, but rarely, a polynuclear leukocyte or a basophilic cell is seen, but no eosinophiles or myelocytes are encountered. The much enlarged glands of Cases II. and IV. show considerable infiltration with erythrocytes. There is considerable proliferation of the endothelium of the sinuses, especially in Case IV. Many of the cells are quite large and conspicuous, and here and there a collection of what appears to be proliferating endothelium is to be seen. Some of the vessel walls of Case IV. show a hyaline or amyloid transformation.

Spleen. In Case I. the spleen was about one-third larger than normally; in Case II. it weighed 400 grams; in Case III. 300 grams; and in Case IV. 1240 grams. Microscopically the lesions are much like those seen in the lymph glands. In general, however, the structure is not so uniform as in the enlarged glands, the distinction between follicles and the pulp being much better preserved; in some cases, especially in Cases I. and IV., it is well preserved. The prevailing cell is the large lymphocyte, but there are relatively many smaller lymphocytes than in the glands. A few polynuclear leukocytes, a rare eosinophile, and an occasional basophile are to be seen. The bloodvessels of the spleen in Cases I. and IV., and to some extent in the other cases, are the seat of hyaline degeneration, and there is some proliferation of the endothelium. There are a number of small hemorrhages in all the cases, but in Case IV. they form a conspicuous feature in the spleen.

Thymus.[1] The enlargement of the thymus formed an interesting feature

[1] Reimann (Ein Fall von acuter Leukämie mit Thymustumor bei einem neunjährigen Madchen, Wien. klin. Woch., 1899, vol. xii. p. 967), reporting a case, has collected the literature on enlargement of the thymus in acute leukemia, a condition which is especially common in young subjects.

of Case II. Microscopically it presents a picture almost entirely analogous to that of the enlarged glands of the same case; that is, the enlarged thymus consists of an almost homogeneous structure made up almost exclusively of lymphoid cells, between which here and there a small amount of delicate connective tissue trabeculæ can be distinguished.

Bone-marrow. The bone-marrow was examined in Case I. (film preparations from a rib), Case II., and Case IV. (film preparations and sections from the ribs and femurs). The examinations were restricted to small bits of marrow, and, the technic being somewhat defective, the lesions are suggestive rather than conclusive. The especially interesting feature is the predominance of large mononuclear non-granular cells. These are of the lymphocyte type and of the large mononuclear leukocyte type found in the circulating blood. Intermediate in type between these there are cells that it is difficult or impossible to classify, and this is also true as regards these cells and a type of cell resembling neutrophilic myelocytes. As a matter of fact, it is very easy to convince one's self of a genetic relationship existing between all of these cells. Typical myelocytes, however, are very few in Cases I. and III.; they are more numerous in Case IV. A few basophiles, an occasional polynuclear leukocyte, and a number of erythrocytes and erythroblasts are seen, but no giant cells are encountered.

Liver. The liver in Case I. was one-fourth larger than normally. In Case II. it weighed 2200 grams, in Case III. 1600 grams, and in Case IV. 1750 grams. The liver cells in general are degenerated; some moderately cloudy, others more cloudy and granular, with poorly staining nuclei, while still others are completely necrotic. The necrosis is more or less widespread in all of the cases, but fairly well circumscribed foci of necrosis are quite apparent. Some of the larger necrotic foci exhibit hemorrhages. Cases I., II., and III. present a general lymphocytic infiltration, intraacinar and interacinar, especially the latter. In many regions the lymphocytic cells, which can be readily identified as similar to the cells present in the circulating blood, are collected into quite large foci, for the most part about the bloodvessels and between the lobules. In Case IV. the liver presents well-marked cirrhosis and gumma formation (which in no essential differs from similar lesions found in other circumstances), and amyloid degeneration (moderate in degree). The mononuclear cellular infiltration is quite marked, both in the newly formed connective tissue (which reveals a number of fibroblasts) as well as elsewhere.

Kidneys. The kidneys in Case I. were about one-half larger than normally. In Case II. they weighed together 400 grams, in Case III. 300 grams, and in Case IV. 650 grams. The epithelial cells lining the tubules are moderately degenerated in all of the cases, especially in the cortex. The organ in general is congested, especially the glomeruli. Extensive lymphocytic infiltration is present in all the cases, but especially in Case II, in which it is massive. In all the cases it is most marked in the cortex, being always intraglomerular, in some regions distinctly periglomerular, but it is usually

rather irregular in distribution. In Case IV. the lymphocytic infiltration is slight and usually about the bloodvessels. The vessels themselves are amyloid, and there is some degree of fibrosis of the entire organ.

Heart. The heart in Case I. was normal in size; in Case II. it weighed 320 grams, in Case III. 120 grams, and in Case IV. 320 grams. The muscle fibers in general are fairly normal; at all events, there is no marked degenerative alterations. Lymphocytic infiltration, widespread, but moderate in degree, is present in Cases I., II., and III., especially in Case III. It is particularly conspicuous about the smaller bloodvessels, but also between the muscle fibers. The pericardium and endocardium appear normal, aside from the hemorrhages already mentioned. Beneath both serous linings there are small foci of lymphocytic infiltration. The heart in Case IV. shows slight fibrosis of the vessels and intermuscular tissues.

Lungs. The lungs in Case I. were normal in size. In Case II. they weighed together 740 grams, in Case III. 580 grams, and in Case IV. 1150 grams. The only noteworthy feature of the lungs are foci of mononuclear cells in moderate number scattered throughout the lungs in all of the cases, especially about the small pulmonary vessels, and to some degree about the bronchioles. They are much larger than is compatible with the idea of their being only the normal lymph nodes found in these situations.

Gastrointestinal Tract. The gastrointestinal tract revealed lesions in all the cases—Cases I. and III, hyperplasia and ulceration of the lymphoid follicles; Cases II. and IV., small hemorrhages, and Case IV., thickening of the pylorus. Especial interest centers in the lymphoid hyperplasia and ulceration of Cases I. and III., which were a noteworthy feature. Microscopically the mucosa and submucosa are extensively infiltrated by lymphoid cells, the entire picture recalling that of the enlarged lymph glands. The cellular infiltration is quite uniform, although here and there indications of germ centers are still apparent. Some slight lymphocytic infiltration is seen between the muscular fibers, and here and there beneath the peritoneum there are small collections of mononuclear cells. The ulceration involves the mucosa and the submucosa, but not the muscularis, being limited to and not extending beyond the lymphocytic collections. The pylorus of Case IV. reveals considerable hyperplasia and fibrosis of the submucosa and muscularis.

The *pancreas, adrenals,* and *voluntary muscles* reveal no noteworthy lesions, except the adrenals of Case II. and IV., which are the seat of moderate lymphocytic infiltration.

The foregoing cases, then, are examples of a disease which, although its etiology is unknown, its nature disputed, and the number of cases reported comparatively small, is nevertheless tolerably well understood clinically. Although each of the cases exhibited individual peculiarities, they exhibited also certain features in common. In Case II. the disease developed suddenly during an apparently normal postpuer-

peral convalescence. In Cases I., III., and IV. the onset was rather subacute, and followed what may be looked upon as a prodromal period, which varied in duration in the different cases and in which increasing weakness and loss of appetite were the only noteworthy symptoms. Without assignable cause each of the patients developed a rapidly progressive cachexia, attended by loss of strength and flesh, irregular fever, dyspnea, rapid pulse, swelling of the mucous membrane of the mouth and the tonsils, and submucous and subcutaneous hemorrhages. The swelling and hemorrhagic infiltration of the mucous membrane of the mouth became a conspicuous feature of Cases II., III., and IV., and much simulated scorbutus. In Cases I. and II. the lymph glands were not enlarged clinically, and at the necropsy Case I. (in which the leukocytes reached 119,500) revealed only moderate swelling of the mesenteric and retroperitoneal glands, and Case II. (in which the leukocytes reached 567,200) revealed only slight enlargement of the lymph glands in general. In Case III. (in which the leukocytes reached 378,000) all of the lymph glands were much enlarged throughout the course of the disease. In Case IV. (in which the leukocytes, at one count as low as 5200, finally reached 37,000) the cervical, axillary, and inguinal lymph glands, just palpable when the patient was admitted to the hospital, became moderately enlarged under observation, and the cervical glands proceeded to suppuration. At the necropsy the inguinal and axillary glands, which were only slightly enlarged, whitish, and quite firm, were in marked contrast to the very much enlarged and reddish glands of the thorax and abdomen. In Cases I., II., and III. the spleen was slightly enlarged, whereas in Case IV. it was considerably enlarged. In all of the cases the diagnosis centered in the lymphocytic condition of the blood.

Case IV., which in some respects differed from the others, presented several interesting features that seem to justify its inclusion here, if for no other reasons than for purposes of discussion. Despite a normal number of leukocytes (9000, 6000, 2500) during the first two weeks that the patient was under observation, there was a high-grade relative and absolute lymphocytosis (98 per cent., 8820, 5760). This being unusually high appeared to render insufficient an otherwise likely diagnosis of syphilis of the liver. The patient had had syphilis and malaria, to which the enlargement of the liver, spleen,

and lymph glands might readily have been attributed. Soon, however, the clinical picture of lymphocytic leukemia declared itself, the relative lymphocytosis continued, absolute lymphocytosis increased (to a maximum of 36,848), and within seven weeks from the time of first observation, within three weeks from the time that the patient considered himself really ill (the time of his second admission to the hospital), he was dead. That this was an ordinary case of lymphocytic leukemia may be open to dispute; that it was an ordinary case of syphilis is also open to dispute; in view of which facts I feel justified in including it in this report. That lymphocytosis is a feature of many cases of syphilitic infection, and that many cases of leukemia have an antecedent history of syphilis, are additional interesting facts in this connection.

Undertaking to study the nature of leukemia, we find that the opinions entertained with regard to it have been considerably modified from time to time, and that they are still unsettled.[1] This is attributable to many factors, but in large part to the imperfections and instability of our knowledge of the histogenesis and interrelations of the different forms of leukocytes—in diseased states even more than in health. Our knowledge is still defective, and considerable confusion has arisen from the multiplicity of names given to like cells and a like name to dissimilar cells; but the results of certain investigations prosecuted during the last several years are extremely suggestive, and warrant at least provisional opinions.

Without reviewing the opinions formerly entertained, it suffices to point out that at the present time two schools[2] contend, as it were, regarding the nature of the disease: (1) that represented by Ehrlich[3]

[1] A review of the literature is scarcely necessary at the present time, especially in view of the fact that at the meeting of this Association in 1898, Fussell, Jopson, and Taylor, reporting two cases, reviewed the literature and collected fifty-seven cases. Additional reviews of the literature have been furnished by Taylor, Studies in Leukemia, Contributions from the William Pepper Laboratory of Clinical Medicine, 1900, pp. 148–328; Müller, Die Morphologie des leukämischen Blutes und ihre Beziehungen zur Lehre von der Leukämie, Centralblatt für allg. Pathologie, 1894, vol. v. pp. 554, 601; and Walz, Zusammenfassendes Referat über die neuere Literatur der Leukämie, Centralblatt für allg. Pathologie, 1901, vol. xii. p. 967. Recently Nichols, American Medicine, vol. v. p. 827, vol. vi. p. 102, reporting two cases, states that he has collected 121 cases from the literature.

[2] The critical observer may insist that there are at least three opinions regarding the nature of leukemia—adding to the two that I shall mention, Löwit's opinion regarding the parasitic nature of the disease. But Löwit's opinion is scarcely entertained other than by himself.

[3] Ehrlich, Lazarus, and Pincus. Die Leukämie, Nothnagel's Specielle Pathologie und Therapie, 1901, vol. viii.

and his followers and (2) that prominently represented by Walz,[1] Pappenheim,[2] Grawitz,[3] Michaelis and Wolff,[4] etc. The views of Ehrlich are, briefly, as follows:

There are two totally distinct forms of leukemia: the one lymphatic (lymphemia), due to primary disease of the lymph glands, and the other, myelogenous (myelemia), due to primary disease of the bone-marrow. The two types of cells—the lymphocytes on the one hand and the myelocytes on the other—are totally distinct, and neither they nor the respective forms of leukemia merge or transform the one into the other. In addition to the morphologic criteria, the distinctions between the two types of cells consist, mainly, in a lower order of biologic characteristics on the part of the lymphocytes—an absence of specific granulations, an absence of marked activity, and a consequent inability to emigrate, absence of bactericidal and phagocytic properties, an absence of peptic and oxidizing ferments, etc.—whence it follows that the biologic significance of the myeloid tissue is much higher than that of the lymphatic tissue. Lymphatic leukemia is a passive leukocytosis, the non-motile lymphocytes being passively swept into the circulation, whereas myelogenous leukemia is an active leukocytosis, the actively motile marrow cells emigrating into the circulation in response to some positive chemotactic stimulus. The lymphomatous foci in the organs are the consequence of secondary heteroplastic metastatic new-formations, and the bone-marrow is the seat of production of the erythrocytes and the place where the mononuclear young forms of the different types of polynuclear leukocytes are gradually developed.

On the other hand, in opposition to Ehrlich's view, Pappenheim and Walz, independently, and, more recently, Grawitz, and Michaelis and Wolff (together and separately), reverting to the older Neumann (or Virchow-Neumann) view, ascribe preponderating importance to the bone-marrow in all cases of leukemia, the lymphatic as well as the myelogenous. They point out, especially, that a number of cases

[1] Loc. cit.

[2] Neuere Streitfragen aus dem Gebeit der Haematologie, Zeitschrift für klinische Medicin, 1902, vol. xlvi. p. 216. (Contains other references.)

[3] Klinische Pathologie des Blutes, 2te Aufl., Berlin, 1902.

[4] Die Lymphocyten, Deutsche medicinische Wochenschrift, 1901, vol. xxxvii. p. 651. Ueber Granula in Lymphocyten, Virchow's Archiv, 1902, vol. clxvii. p. 151. Wolff, Ueber die Bedeutung der Lymphoidzelle bei der normalen Blutbildung und bei der Leukämie, Zeitschrift für klinische Medicin, 1902, vol. xlv. p. 385.

of lymphatic leukemia have been observed with slight or no noteworthy changes in the lymph glands, that clinically as well as anatomically the sharp distinction between the two forms of the disease made by Ehrlich is impossible, and that there is no case, carefully studied, that has not revealed changes in the bone-marrow, thus confirming the opinion first expressed by Neumann. The discussions on the subject have now resolved themselves into the question whether the disease is of single or of dual origin, whether it is always myelogenous—the two clinical types (based upon the blood picture) being due to involvement of the lymphoid or the myeloid constituents of the bone-marrow in the individual case—or whether it is sometimes lymphatic and sometimes myelogenous (Ehrlich, Lazarus, and Pincus). In this connection, however, it is worthy of observation that, recently, Pincus has so far modified the original Ehrlich conception of the disease as to include the lymphoid constituents of the bone-marrow among the points of departure of the disease. The solution of the question at issue depends, in part at least, upon one's conception of the lymphocyte, which, itself, is much involved in the more or less obscure subject of the histogenesis of the blood, especially of the leukocytes.

At the present time the greatest interest centers in the large mononuclear leukocyte (as distinguished from the large lymphocyte), and in the lymphoid constituents of the bone-marrow. Commonly mononuclear non-granular cells with a slight amount of basophilic protoplasm are classed as lymphocytes, and their variations in size determine some observers to distinguish between a large lymphocyte and a small lymphocyte, although other observers frankly confess their inability to classify in either of these groups a number of such cells that really are intermediate in size between the so-called small and the so-called large lymphocyte. In addition to these, however, normal blood contains a few (usually 1 to 4 per cent., rarely 6 to 8 per cent.) of mononuclear non-granular cells that are much larger than the large lymphocyte (sometimes measuring 18μ to 20μ in diameter), that have an eccentrically situated, pale, irregularly spheroid or ovoid (sometimes indented) nucleus, and a relatively large amount of slightly basophilic non-granular protoplasm. Ordinarily, especially by means of the Ehrlich stain, these cells are scarcely to be distinguished from the large lymphocyte, but certain of the newer combinations of methyl-

ene blue and eosin furnish assurance of what formerly was largely conjecture. In well-differentiated cells the large mononuclear leukocyte may be distinguished from the large lymphocyte by the fact that it is much larger, that its nucleus though large is relatively small as compared with the protoplasm, that there is considerable protoplasm, and that the protoplasm is less basophilic than the pale nucleus—in contrast with the lymphocyte, in which the protoplasm is more basophilic than the nucleus.

A variety of opinions are entertained with regard to this cell and its relations to the other cells in the blood and blood-forming organs. Ehrlich is not certain of its place of origin, although he inclines to look upon it as myelogenous in origin, and he states that it is the precursor of the so-called transitional cell and the polynuclear neutrophile.

The opinions recently expressed by Pappenheim, Walz, Grawitz, Michaelis and Wolff and others, have attracted considerable attention and demand further investigation. Thus Pappenheim, who takes an extreme view opposed to Ehrlich, states that the large lymphocyte is the mother-cell of all forms of leukocytes, the characteristic parenchymatous cell of all reticular tissue, and a cell, therefore, present in the bone-marrow (a reticular tissue). He believes that leukemia consists of a proliferation of such reticular tissue, and that in consequence lymphocytes must be found in all cases of leukemia—even the myeloid, there being no such thing as a pure granulocytic leukemia. Pincus' hypothesis that there is in the bone-marrow a special lymphoid tissue, proliferation of which results in lymphocytic leukemia without enlargement of the glands and the spleen, is to be abandoned; on the contrary, Pappenheim believes that in every case of lymphocytic leukemia the proper lymphoid cells of the bone-marrow proliferate, and that in consequence of this the myeloid tissue becomes the seat of lymphadenoid degeneration and as myeloid tissue disappears. In contradistinction to Ehrlich, he believes that the enlargement of the lymph glands is of subsidiary importance in leukemia, even in cases in which it is the initial manifestation—in which cases he looks upon it as proleukemic or pseudoleukemic. While disposed to agree with Ehrlich that the lymphocytes of normal blood and of the lymphocytosis of pseudoleukemia may come from the lymph glands, he denies that the enormous increase of lymphocytes seen in

leukemia can be due to glandular alterations. On the contrary, he believes that these lymphocytes come from the bone-marrow, and that the bone-marrow plays the principal rôle in all cases of leukemia—the so-called lymphatic as well as the myelogenous, and the lymphatic whether or not it be attended by enlargement of the lymph glands. He rejects Ehrlich's classification of leukemia into a lymphatic and a myelogenous form, as well as Pincus' modification of this classification—a lymphoid and a myeloid form, preferring the terms lymphocytic and mixed-cell to designate the two well-known forms of the disease. According to the blood picture, he distinguishes a lymphocytic pseudoleukemia, due to proliferation of lymphoid tissue diffuse in the glands or the spleen or circumscribed in the bone-marrow; a lymphocytic leukemia, due to diffuse proliferation, not of the lymphoid portion of the bone-marrow, but (as he prefers to express it) of the lymphadenoid degenerated myeloid tissue; and a mixed-cell leukemia, due to diffuse proliferation of the normal specific myeloid tissue. Pseudoleukemia, therefore, is lymphocytic, and every leukemia is myelogenous, a myelemia. As Pappenheim expresses it, myeloid proliferation is always myelogenous and leads always to mixed-cell leukemia; lymphoid proliferation in the glands and spleen leads to pseudoleukemia; if, however, it is diffusely myelogenous it leads to leukemia—lymphocytic leukemia. That the leukemic blood picture result, it is believed that it is not necessary that the entire bone-marrow become hyperplastic; diffuse proliferation in circumscribed areas suffices. For instance, the long bones may remain free; if the epiphyses do not proliferate into the fatty marrow, the latter does not become pyoid, and the proliferating red lymphoid marrow remains macroscopically and microscopically normal. Pappenheim further believes that inasmuch as in many cases it is difficult to make a definite diagnosis from the blood picture or the clinical course of the disease, certainty is to be obtained only by a microscopic examination of the bone-marrow. He believes also that in nature lymphocytic leukemia and pseudoleukemia are identical and related disease processes—both resulting from lymphoid proliferation and revealing like blood findings—lymphocythemia; they differ, however, in situation and the blood findings thus differ quantitatively. Lymphocytic leukemia and mixed-cell leukemia, on the other hand, are diffuse bone-marrow processes, related only in situation—whence in both the

enormous increase of leukocytes in the blood; qualitatively, however, the blood shows that they differ pathogenetically and in nature, that in the one there is lymphoid proliferation, and in the other myeloid proliferation—the blood picture being a mirror of the then existing hyperplastic or metaplastic-hyperplastic marrow changes. In addition to lymphocytic and mixed-cell leukemia, Pappenheim further distinguishes intermediate and atypical forms, based upon the view that the lymphocytes and the leukocytes are not two heterogeneous formations without genealogic relationship, but rather descendants of one medullary cell family. As a subvariety of lymphocytic leukemia he speaks of a form in which in addition to lymphocytes large mononuclear leukocytes in large numbers occur in the bone-marrow and the blood, a condition due to what he describes as a splenoid metaplasia of the bone-marrow—a splenoid myelemia. As atypical forms of leukemia he designates cases of mixed-cell leukemia in which, in addition to lymphocytes and non-granular mononuclear leukocytes, one or the other variety of granulocytes (but not all three varieties) occur in the blood, the marrow, and the so-called metastases. On the one hand, these atypical, intermediate, or mixed cases represent an advanced stage of development of lymphocytic leukemia—lymphocythemia with myelocytosis, and, on the other hand, an incomplete mixed-cell leukemia—mixed-cell leukemia without eosinophiles and mast-cells, that is, also myelocytes and lymphocytes. Inasmuch as lymphoid tissue contains more lymphocytes than mononuclear non-granular leukocytes, splenoid tissue, more leukocytes than lymphocytes, and myeloid tissue, more myelocytes and granulocytes than non-granular leukocytes and lymphocytes, the following differences in the blood picture occur: (1) Only lymphocytes or at the most associated with a few mononuclear leukocytes; (2) lymphocytes and many leukocytes, to which (3) may be added as representatives of the myeloid type one or all three forms of myelocytes. Pappenheim also states that only the lymphocytic and the atypical splenoid lymphocytic leukemia, when they do not arise primarily, may develop out of lymphatic, splenic, and even primary myelogenous pseudoleukemia; and that the other typical and atypical forms of mixed-cell leukemia are always primarily myelogenous. Finally, Pappenheim summarizes the differences between his opinion and those of Ehrlich and of Pincus, as follows:

(A) Ehrlich.

1. Lymphatic leukemia: Lymph-gland changes, followed by the blood changes, possibly followed by lymphadenoid bone-marrow changes.
2. Myelogenous leukemia: Bone-marrow changes, followed by the blood changes, possibly followed by myeloid lymph-gland changes.

(B) Pincus.

1. Lymphoid leukemia:
   (*a*) Ordinary cases: Lymph-gland changes, followed by the blood changes, possibly followed by bone-marrow changes.
   (*b*) Cases without enlargement of the lymph glands: Bone-marrow changes, followed by the blood changes.
2. Myeloid leukemia: Bone-marrow changes, followed by the blood changes, possibly followed by lymph-gland changes.

(C) Pappenheim (according to whom bone-marrow changes always precede the blood changes).

1. Lymphocytic leukemia:
   (*a*) Ordinary cases: Pseudoleukemic enlargement of the lymph glands, followed by the bone-marrow changes, followed by the blood changes.
   (*b*) Cases without enlargement of the lymph glands: Bone-marrow changes, followed by the blood changes.
2. Mixed-cell leukemia: Bone-marrow changes, followed by the blood changes, possibly followed by lymph-gland changes.

Pappenheim gives the following as his opinion regarding the cytogenesis of normal and of leukemic blood:

(A) Normal blood.

(*a*) The polynuclear granular α, γ, ε cells are derived exclusively from the bone-marrow.

(*b*) The mononuclear, non-granular, large leukocytes are derived from both the bone-marrow and the spleen, possibly, also, from the lymph nodes.

(*c*) The mononuclear, non-granular, small lymphocytes are derived mostly from the lymph glands; in part, also, from the follicles of spleen, and they may be swept into the circulation from the bone-marrow.

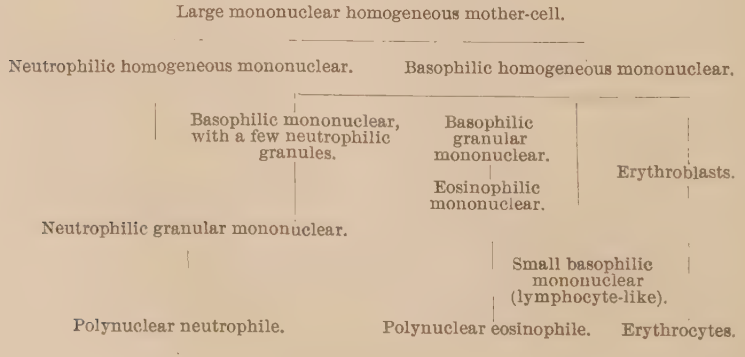
(B) Leukemic blood.

(*a*) The heterotopic cells found in the blood in mixed-cell leukemia, such as the large, mononuclear, non-granular lymphocytes and the granular myelocytes are derived almost exclusively from the bone-marrow, but in small numbers from the existing metastases.

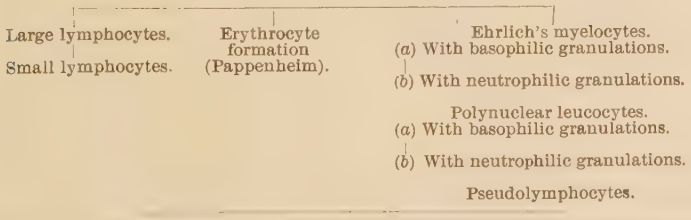
(*b*) The quantitatively increased polynuclear, granular cells of mixed-cell leukemia are likewise derived almost exclusively from the bone-marrow, but a few, however, from the metastases.

(*c*) The quantitatively increased mononuclear, non-granular, large leukocytes and the small lymphocytes in mixed-cell leukemia and in lymphocytic leukemia are derived in preponderating number from the bone-marrow; in very small numbers, also, from the spleen, the lymph glands, and the metastases.

Walz and Grawitz, in many respects, are in practical concurrence with Pappenheim, but there are minor differences of opinion. Thus, Grawitz looks upon the large mononuclear leukocyte as the mother-cell of the other leukocytes, and speaks of it as an "unripe" or "immature" cell, ordinarily capable of further differentiation into either the ordinary basophilic cell, or, by the assumption of neutrophilic granulations, into a neutrophilic myelocyte; and he states that from its appearance in the blood in leukemia no one is able to say to which of its two later stages of development it would have progressed had it not been arrested at an earlier period in its life history—whether it would have become a myelocyte (in the ordinary sense) or a lymphocyte (in the ordinary sense). He believes the blood corpuscles to be developed according to the following scheme:



Wolff states that recent investigations tend to invalidate the opinion that the lymphocytes can be differentiated from the granulocytes, especially inasmuch as these investigations have demonstrated that the lymphocytes contain granules[1] and are actively motile, and because of findings that indicate the probability of the occurrence of an active lymphocytosis. Insisting upon the presence of a cell described by Michaelis and himself as an "indifferent lymphoid" cell,[2] he says that, although morphologically similar to the lymphocyte, it is capable of further differentiation, and that the indifferent lymphoid cell of the bone-marrow, in most of its stages of development, can be distinguished morphologically from the lymphocyte. Michaelis and Wolff believe that considerable confusion has arisen because the term lymphocyte has not been sufficiently restricted in its application, and they suggest its restriction to what is ordinarily understood by a lymphocyte (Ehrlich's); that is, a cell incapable of further differentiation. Thus, the future of the cell serves as a basis of distinction from the lymphoid cell. Wolff further believes that in postembryonal life under normal conditions in man the different organs of the hematopoietic system have special functions; that is, the bone-marrow forms granulocytes; the lymph glands, lymphocytes; whereas the spleen, in addition to forming large mononuclear cells, is concerned especially with phagocytosis. All of these organs, however, contain indifferent lymphoid cells which, under certain conditions, may act vicariously for one another. Furthermore, the spleen is believed normally to possess a myeloid function. Wolff further believes that the indifferent lymphoid cell is the mother-cell of all of the blood corpuscles, and that the development is according to the following scheme:



[1] Michaelis and Wolff. Ueber Granula in Lymphocyten, Virchow's Archiv, 1902, vol. clxvii. p. 151.

[2] Apparently identical with the large mononuclear leukocyte, Grawitz's unripe cell, Naegeli's myeloblast, and Benda's myelogonie—an unfortunate series of names for identical or morphologically similar cells.

Wolff believes, and bases his belief upon a case that he reports, that the two forms of leukemia, the lymphatic and the myelogenous, may merge or be transformed the one into the other. In the case reported a large number of the large lymphocytes exhibited deviations from the normal appearances of the lymphocytes—from which he feels justified in concluding that these cells represent stages of development of the indifferent lymphoid cell, and that the case represents what he proposes to call a "lymphoid-cell" leukemia. He distinguishes, therefore, three varieties of leukemia; or, as he prefers, he refers both of the ordinarily understood forms of leukemia to this so-called lymphoid-cell leukemia, believing that from this, either a pure lymphatic or a pure myeloid leukemia may develop. This, he admits, is only theory, but he believes that it is certain that in addition to the two usual forms of leukemia, a third transitional form, or a lymphoid-cell leukemia, exists. Finally, he states that leukemia is not a manifestation of tumor formation with metastases, but that it is a metaplasia of the hematopoietic organs, arising from unknown causes.

Somewhat at variance with the foregoing are Rubinstein's[1] views regarding the histogenesis of the blood. Thus, he states that the granular cells of the blood are derived from the homogeneous large mononuclear cells of the bone-marrow by the formation in their protoplasm of granules which in the beginning are basophilic, and that the maturation of young, non-granular forms to older granular forms takes place exclusively in the bone-marrow, not in the circulating blood. He believes, also, that the large, homogeneous, mononuclear leukocytes are derived from the small lymphoid cells present in every bone-marrow —cells that he looks upon as the mother-cells. These lymphoid cells of the bone-marrow are said to be developed *in situ*, and to be in no way related to the lymphocytes of the lymphatic system, whence Rubinstein believes that the Uskoff teaching is untenable. This lymphoid cell of the bone-marrow is also believed to be the mother-cell of the eosinophilic leukocytes, as well as of the pseudoeosinophilic or neutrophilic leukocytes, but transitions from the neutrophiles to the eosinophiles are not to be observed either in the blood or the bone-marrow. The development of the leukocytes in the bone-marrow,

[1] Ueber die Veranderungen des Knochenmarks bei Leukocytose, Zeitschrift für klinische Medicin, 1901, vol. xlii. p. 161.

according to Rubinstein, therefore, is as follows: 1. Small lymphoid cells with nuclei of well-defined structure, and a narrow rim of distinctly basophilic, non-granular protoplasm. 2. Larger lymphoid cells, with large nuclei of well-defined structure, and a wide rim of granular protoplasm. 3. Large lymphoid cells, with nuclei that stain well, but have not such a well-defined structure, and a wide rim of non-granular protoplasm. 4. Mononuclear, non-granular leukocytes, large lymphoid cells, with a palely staining round nucleus, and pale, non-granular protoplasm. 5. Myelocytes, mononuclear leukocytes, with round nuclei and granular (in man neutrophilic) protoplasm. 6. Polynuclear leukocytes, with polymorphous or multiple nuclei, and neutrophilic granular protoplasm. (In rabbits instead of the neutrophilic there are pseudoeosinophilic granules.) 7. The eosinophilic cells go through similar stages of development, with this difference, however, that the granules from the beginning are larger, and soon show, instead of a neutrophilic, an eosinophilic reaction.

Without detailing the opinions or the results of the investigations of other workers, it will suffice to say that evidence has been for some time accumulating that tends seriously to invalidate Ehrlich's contention relative to the entire dissimilarity of the two clinical types of leukemia. A fact of special significance in this connection is that there is no longer any doubt that the bone-marrow is to be reckoned with the lymphoid structures of the body. As a matter of fact, the lymphoid construction of the bone-marrow has been emphasized by many writers since Arnold[1] first definitely pointed it out—thus, the writers previously mentioned, as well as Muir,[2] Dorothy Reed,[3] Brinckerhoff and Tyzzer,[4] etc. The bone-marrow is most correctly described as consisting (in addition to a capillary plexus) of a delicate reticular network, the meshes of which support a variety of cells that have been variously described, but among which it is possible to distinguish those definitely of the erythroblastic series, those of the leukoblastic series, giant cells, and certain lymphoid cells which for

[1] Zur Morphologie und Biologie der Zellen des Knochenmarks, Virchow's Archiv, 1895, vol. cxl. p. 411.

[2] On the Relation of the Bone-marrow to the Leukocyte Production and Leukocytosis, Journal of Pathology and Bacteriology, 1901, vol. vii. p. 161.

[3] A Case of Acute Lymphatic Leukemia, without Enlargement of the Lymph Glands, Amer. Journ. Med. Sciences, 1902, vol. cxxiv. p. 653.

[4] On the Leukocytes of the Circulating Blood of the Rabbit, Journ. Med. Research, 1902, vol. vii. p. 173. On Amphophile Leukocytogenesis in the Rabbit, ibid., 1902, vol. viii. p. 449.

want of a better name may be spoken of as undifferentiated lymphoid cells. These cells, as well as certain of the non-granular young forms of the leukoblastic series, are indistinguishable from, indeed, they appear to be identical with, the lymphoid cells of the lymph glands and other lymphoid nodes in the body. Thus, as suggested by Walz, the bone-marrow may be looked upon as a modified reticular tissue capable of forming not only lymphocytes, but granulocytes as well. The lymphoid structure of the bone-marrow, at least that the bone-marrow contains lymphoid constituents, is admitted by Pincus, despite its quite obvious corollary.

The transition of normal bone-marrow tissue into the lymphadenoid tissue characteristic of lymphocytic leukemia is variously explained. As is well known, Ehrlich looks upon it as a form of metastasis—a view combated by Pappenheim, as already pointed out, who believes that in lymphocytic leukemia the bone-marrow becomes the seat of lymphadenoid degeneration in consequence of proliferation of its proper lymphoid cells, and as myeloid tissue disappears. Walz believes that the transition of the bone-marrow into the lymphadenoid tissue characteristic of lymphocytic leukemia is best explained by assuming that the granulocytes being ameboid have simply left their home or normal abiding place. The more reasonable of the opinions, however, is that given by Pappenheim.

Inasmuch, then, as the bone-marrow is unquestionably to be included among the lymphoid structures of the body, the inference is quite natural that it may form lymphocytes.[1] And that lymphocytes, at all events, cells indistinguishable morphologically, tinctorially, and biologically from the lymphocytes of the lymph glands and of the circulating blood, are formed in the bone-marrow can no longer be doubted. The evidence on this point seems conclusive: that adduced by the writers previously mentioned, and of which my own small amount of work is confirmatory. Probably the most conclusive evidence has been furnished by certain diseased states, especially cases of acute lymphocytic leukemia without enlargement of the lymph glands—of

[1] When we proceed to derive lymphocytes from the bone-marrow, we open up the possibility of considerable confusion in the use of our descriptive terms, since in this event lymphocytes are myelocytes in a wide sense—that is, bone-marrow cells. The terms lymphocyte and myelocyte, however, have become so restricted by usage to certain definite and well-recognized cells that it is probably better to continue to use them, despite the slight inaccuracy from a histogenetic point of view, rather than to introduce new terms and make confusion worse confounded.

which a number have now been reported by Pappenheim, Walz, Reed, Michaelis and Wolff, previously mentioned, as well as by Hirschlaff,[1] Körmöczi,[2] Spencer,[3] Hayem and Bensaude,[4] myself herewith, and others. In these cases, inasmuch as the blood contained large numbers of lymphocytes, in some cases enormous numbers, one of my cases revealing 551,319 lymphocytes to the cubic millimeter of blood; as the lymph glands, both macroscopically and microscopically, in some cases showed no deviations from the normal, in other cases but slight deviations; and as the bone-marrow revealed lymphadenoid metamorphosis in all cases in which it was carefully studied, the very obvious inference is to attribute the formation of the enormous numbers of lymphocytes to the diseased bone-marrow. It is not necessary, however, to believe that these lymphocytes are formed only in the bone-marrow. Although it is likely that in most of the cases of lymphocytic leukemia the great majority of the circulating lymphocytes, in some of the cases all of the circulating lymphocytes, are formed in the bone-marrow, I am inclined to believe that they may be developed from any of the lymphoid tissues of the body that present the requisite alterations, such as the lymph glands, the other lymphoid nodes, as in the intestines, the thymus, and even the so-called metastases. The confusion occasioned by Michaelis and Wolff attempting to restrict the term lymphocyte to a cell morphologically identical with their indifferent lymphoid cell, but a cell incapable of further differentiation, is somewhat to be deprecated, since no one can be expected to determine from the appearances and other characteristics of a cell found in the circulating blood or in the bone-marrow what its future would have been had it not been arrested at an early period of its development. My own tentative opinion harmonizes with that of Grawitz on this point, and I am inclined to believe that the cells known as lymphocytes, whether they arise in the bone-marrow or elsewhere in the body, are so closely related biologically, as well as morphologically, that attempts to differentiate them are likely to prove futile. As far as normal blood is concerned the matter is simple, since all the lymphoid cells found in the normal circulating blood are lympho-

[1] Ueber Leukämie, Zentralblatt für innere Medizin, 1898, vol. xix. p. 837.

[2] Das hämatologische Bild der Lymphämie ohne anatomische Befund, Deut. med. Woch. 1899, vol. xxv. p. 238.

[3] A Case of Lymphatic Leukemia, Lancet, 1900, vol. i. p. 926.

[4] Leucémie aiguë à forme hémorragique, La Médecin Moderne, 1903, vol. xiv. p. 56.

cytes; in lymphocytic leukemia, however, the question is more complicated, and needs further elucidation.

Bearing directly upon this question, and in themselves of the very greatest interest and importance, are the results of certain investigations conducted by Flexner[1] and his pupil Bunting.[2] The investigations were undertaken with a view to study the histologic changes in the lymph glands, spleen, and bone-marrow following the experimental injection of cytotoxic serums derived by immunization against these tissues, as well as the associated changes in the circulating blood. It was thought that the employment of cytotoxins in this manner might assist in determining the interrelationship of the several types of tissue concerned in the dispute as to the presence in the bone-marrow of lymphoid tissue or of a common ancestral cell from which both lymphocytes and granulocytes might be developed. As a result of his investigations, Flexner states that "while all the lymphatic tissues respond to the lymphotoxin and myelotoxin, yet the character of the response of the bone-marrow appears to be different—in fact, or, at least, in degree. While, therefore, the reaction of lymph gland, intestinal lymphoid tissue, and spleen to bone-marrow toxin is remarkable, the response of the marrow to lymphotoxins and splenotoxins is far less marked. There would, therefore, seem to be a peculiar potency in the myelotoxin which can only be explained by its possession of numerous amboceptors common to lymphoid cells, and, hence, capable of stimulating that tissue, wherever it exists, to activity. On the other hand, the smaller response of the bone-marrow to the foreign cytotoxins must depend upon its possession of a smaller number of cells with the corresponding receptors for fixation of the amboceptors of these serums. That the bone-marrow contains any such receptors is of interest at the present time on account of the doubt which still exists regarding the lymphoid structure of marrow." The especially interesting and important result of the investigations is, as pointed out by Flexner, the fact "that the bone-marrow under the influence of lymphotoxin responds with an increase of mononuclear non-granular cells, and under the influence of myelotoxin with

[1] The Pathology of Lymphotoxic and Myelotoxic Intoxication, University of Pennsylvania Medical Bulletin, 1902, vol. xv. p. 287.

[2] The Effects of Lymphotoxin and Myelotoxin on the Leukocytes of the Blood and on the Blood-forming Organs, ibid., 1903, vol. xvi. p. 200.

a new production of granular mononuclear and polymorphonuclear cells."

Bunting's studies lead, in part, to the following conclusions: "The amphophile, eosinophile, and basophile leukocytes are derived from the marrow. The lymphoid cells are chiefly derived from the lymph glands and spleen. The marrow, however, is a lymphoid tissue and contains typical lymphocytes. The lymphocyte is ameboid. Amphophile and eosinophile myelocytes may multiply by mitosis. Their number may also be increased by the development of specific granules in the protoplasm of large mononuclear elements with scant basophilic protoplasm, the least differentiated cell of the marrow and identical in appearance with the cells of the germinal centers of the lymph glands. Basophilic cells are formed by the development of basophilic granules in mononuclear cells. Multiplication by mitosis is not excluded by negative findings. Megaloblasts are a constituent of normal marrow and form the proliferating center of erythroblastic tissue."

With regard to the lower order of biologic characteristics postulated by Ehrlich concerning the lymphocyte, and evidenced by the absence of specific granulations and an absence of ameboid activity, one may well concede a difference between the lymphocytes and the granulocytes; they are not identical cells. But that the difference is one of degree only, that it is quantitative rather than qualitative, is suggested by the investigations of Michaelis and Wolff, previously alluded to, by which they demonstrated the presence of granules in lymphocytes—a demonstration that has led Pappenheim to state that we shall have to distinguish between granular and non-granular lymphocytes. Ehrlich and his pupils, however, are not disposed to concede the specificity of the granules—a specificity akin to that of the granulocytes. Furthermore, that the difference between the lymphocytes and the granulocytes is to some extent, at least, quantitative is indicated by the fact that many investigators who have studied the subject attentively believe the lymphocytes to be ameboid, and there is some evidence of the occurrence of an active lymphocytosis. Dr. William H. Welch[1] has for a long time held the opinion and has taught that the lymphocytes are ameboid. I have alluded above to a

[1] Personal communication. See also in the discussion on this paper.

similar opinion entertained by Flexner and Bunting. The activity of the lymphocytes appears to have been quite conclusively proved by Maximow[1] and by Almkvist,[2] and Hirschfeld[3] states that he has observed activity of the lymphocytes in a case of lymphocytic leukemia. It is proper, however, to state that Reckzeh[4] was unable by the methods that he employed to demonstrate evidences of ameboid movement on the part of the lymphocytes; and Mosse,[5] although he was able to study the passage of lymphocytes through the walls of the vessels, the veins as well as the capillaries, was unable, on account of his methods of investigations (fixed and stained preparations), to state whether this passage was active or passive—disposed as he was to believe that it could be passive. However, a lymphocytosis that there is some evidence to believe may be an active lymphocytosis has been observed in certain diseased states, such as tuberculosis, syphilis, pertussis, malignant disease, etc.; a lymphocytosis occurs in certain diseases of the lymph glands, such as pseudoleukemia, in which, however, contrary to the opinion of Pincus and others, it is not constant, and it may not be active; and it is quite reasonable to interpret the great increase in the lymphocytes occurring in lymphocytic leukemia as an active process developing in response to some chemotactic influence.

Finally, of interest as bearing upon the myelogenous origin of all cases of leukemia, the myelocytic as well as the lymphocytic, is the occurrence of intermediate or mixed cases (lymphocytic-myelocytic leukemia), and the still rarer occurrence of cases of acute myelocytic leukemia. The intermediate cases—that is, cases revealing both lymphocytes in large numbers and myelocytes, or cases revealing first the one and then the other blood picture—have been discussed in detail by Pappenheim, Walz, Michaelis,[6] and others previously mentioned. Myelocytes occurred in Cases I. and IV., herewith re-

[1] Experimentelle Untersuchungen über die entzündliche Neibildung, Ziegler's Beiträge, 5tes Supplementheftes, 1902.

[2] Ueber die Emigrations-fähigkeit der Lymphocyten, Virchow's Archiv, 1902, vol. clxix. p. 17.

[3] Sind die Lymphocyten amoeboider Bewegung fähig? Berl. klin. Woch., 1901, vol. xxxviii. p. 1019.

[4] Klinische und experimentelle Beiträge zur Leukämiefrage, Zeitschrift für klin. Med., 1903, vol. i. p. 34.

[5] Zur Histogenese der lymphatischen Leukemie, Zeitschrift für klin. Med., 1903, vol. l. p. 70.

[6] Ueber einen der Gruppe der Leukämieartigen Erkrankungen zugehörigen Fall, Zeitschrift für klin. Med., 1902, vol. xlv. p. 87.

ported, and Fowler,[1] reporting a case, reviews the related literature. Such cases tend to suggest the thought of a close genetic relationship between both varieties of leukemia—a similarity in place of development, if not in nature. As is well known, in cases of myelocytic (myeloid, myelogenous, splenomedullary) leukemia the blood reveals, in addition to neutrophilic and eosinophilic myelocytes and mast-cells, also a large number of typical lymphocytes—non-granular mononuclear cells with a narrow rim of basophilic protoplasm. We are thus unable to conceive of any case of leukemia without an increase of lymphocytes in the blood (in myelocytic leukemia a marked absolute increase if not a relative increase). There is no such thing as a pure granulocytic or myelocytic leukemia. We are thus unable to dissociate an increase of lymphocytes from known proliferation of the bone-marrow. The question at issue, however, becomes very much simplified when we look upon certain non-granular cells of the bone-marrow as indifferent or unripe cells capable of further differentiation into lymphocytes on the one hand and into myelocytes on the other hand.

Contrary to the view formerly entertained, there can scarcely be any doubt of the occurrence of cases of acute myelocytic leukemia, rare though they be. Cases have been reported by Van der Wey,[2] Ewing,[3] Hirschfeld,[4] Grawitz,[5] Türk,[6] and the subject has recently been discussed by Billings and Capps.[7] Most of the cases depart more or less from the commonly accepted characteristics of myelocytic leukemia, especially as laid down by Ehrlich, but probably this is no more than might be expected of an unusual and rare type of disease, as yet but very little studied.

Conclusions. The present state of our knowledge seems to warrant the following opinions: The clinical manifestations and the blood

[1] On the Occurrence of a Form of Leukemia intermediate in Type between the Lymphatic and the Splenomedullary Forms, with Notes of a Case in a Child of Five Years, International Clinics, 1903, 13th series, vol. iii. p. 217.

[2] Beiträge zur Kenntniss der Leukämie, Deut. Archiv für klin. Med., 1896, vol. lvii. p. 287.

[3] Clinical Pathology of the Blood, 1901.

[4] Ein bisher noch nicht beobachteter Befund bei einem Fall von akuter (myeloider?) Leukämie, Berl. klin. Woch., 1902, vol. xxxix. p. 231.

[5] Loc. cit., pp. 318, 332.

[6] Ein Fall von akuter myeloider Leukämie, Zentralblatt für innere Medizin, 1903, vol. xxiv. p. 336.

[7] Acute Myelogenous Leukemia, American Journal of the Medical Sciences, 1903, vol. cxxvi. p. 375.

pictures of leukemia justify the almost universally employed division into two clinical varieties, generally called the lymphatic and the myelogenous (or splenomedullary). Since, however, it has been demonstrated that the so-called lymphatic leukemia may occur with little or no alterations in the lymph glands; since, furthermore, there is good evidence for believing that, whether or not there be enlargement of the lymph glands, the typical leukemic blood picture does not develop until the bone-marrow becomes affected; since, therefore, the bone-marrow lesions appear to be the essential lesions and both varieties of leukemia are myelogenous in origin, the terms lymphatic and myelogenous are scarcely appropriate. The terms lymphoid and myeloid suggested by Pincus are less objectionable, but my preference is for lymphocytic and myelocytic as suggesting the distinguishing features of the bone-marrow proliferation and of the blood in both classes of cases. I am inclined to prefer myelocytic to mixed cell suggested by Pappenheim and by Grawitz, especially as, strictly interpreted, both forms of leukemia reveal a variety of cells in the bone-marrow and the blood, and are therefore mixed-cell leukemias, the myelocytic form, however, as is well known, revealing a greater variety of cells than the lymphocytic. Although, as observed, there are two forms of the disease, more strictly there are extremes of type; but there is no very sharp line of demarcation between them. Atypical and transitional (intermediate or mixed) forms—the merging of one form into the other—do occur, and while we have hitherto thought that acute leukemia is always lymphocytic and chronic leukemia either lymphocytic (the rarer form) or myelocytic (the more common form), apparently trustworthy evidence has recently accumulated that tends to show that acute leukemia may be, though rarely, myelocytic, and, contrary to the rule, certain of the chronic lymphocytic cases reveal an unusually large number of large lymphocytes, and some of the apparently acute cases may be of the small lymphocyte type. The disease, probably in all cases, results from proliferation of the bone-marrow, the blood picture in the individual case being a mirror of the then existing marrow condition, lymphocytic or myelocytic, as the case may be. It is quite likely, however, that some of the circulating lymphocytes in lymphocytic leukemia are formed in the lymphoid structures elsewhere in the body, such as the lymph glands, the lymph nodes, as in the intestine, the thymus, and even the so-called

metastases; but that disease of the lymph glands alone ever gives rise to leukemia may well be doubted. The proliferation of the bone-marrow and the outpouring of the enormous numbers of leukocytes into the blood is doubtless to be referred to chemotactic influences in all cases, the lymphocytic, probably, as well as the myelocytic—that is, the disease is probably always an active leukocytosis. The differences in the clinical course of the disease, as well as in the blood picture (the reaction of the bone-marrow), is probably attributable to differences in the chemotactic agent, whatever it may be, whether an infection or an intoxication. A more or less intimate relationship between the two forms of the disease—the lymphocytic and the myelocytic—is suggested by the fact that both are myelogenous; that the lymphocytes (at least some of them) have granules in their protoplasm, granules probably not identical with the granules of the better-known granulocytes, but possibly of like nature; that the lymphocytes are certainly ameboid, and by the gradually accumulating evidence that tends to show that both lymphocytes and granulocytes are derived from a common ancestor in the bone-marrow. The exact sequence of events in this process is still a matter of dispute and of some speculation. Tentatively, I am inclined to attach much importance to the large mononuclear non-granular cell of the bone-marrow, believing it capable, under the influence of divers stimuli, of assuming either basophilia of its protoplasm and becoming a large lymphocyte (the cell so numerous in the blood in lymphocytic leukemia) or of assuming neutrophilic granules and becoming a myelocyte (in the ordinary sense). Probably its development in one of the other of these directions is influenced by the nature of the chemotactic agent concerned; possibly time has something to do with it, since the basophilic cells are to be looked upon as younger forms, while the neutrophilic myelocytes and their derivatives—the polynuclear neutrophiles—are of an older growth. This opinion is not invalidated by the occurrence of small basophilic cells in cases of chronic lymphocytic leukemia, since these cells also are of an older growth, being the derivatives of the larger basophiles. The genetic relationship between the large mononuclear leukocyte, the large lymphocyte, and the neutrophilic myelocyte was suggested in my cases by morphologic similarities and by the occurrence of neutrophilic or amphophilic granules in basophilic cells. Aside from the granules and basophilia

of the protoplasm the cells might have been either lymphocytes or myelocytes. However the matter may be finally determined, there may be something in the suggestion of an incomplete, imperfect, or pathologic differentiation of certain indifferent lymphoid cells developing under the influence of certain morbid causes at present ill understood. The development, however, is along certain fairly-well defined lines—that is, a lymphocyte does not develop into a myelocyte, nor *vice versa*. At present there is no way of distinguishing, when found in the circulating blood, the lymphocyte derived from the lymph glands from that derived from the bone-marrow. However, the lymphocytes found in the circulating blood in health are probably derived entirely from the lymph glands, whereas those present in lymphocytic leukemia are derived in large part, in some cases exclusively, from the bone-marrow.

It is scarcely opportune at the present time to discuss the relationship, or presumed relationship, between leukemia, pseudoleukemia, certain cases of lymphocytosis, and other diseases of the lymph glands. Recently, as I have already pointed out, a number of writers, of whom Pappenheim may be considered the most extreme, have contended that pseudoleukemia and lymphocytic leukemia are quite related processes. There can be no doubt that the term pseudoleukemia has heretofore comprised a series of diverse diseases of the lymph glands, all of which are much in need of elucidation. Thus, some of them probably are tuberculous in nature, to which aspect of the subject Sailer[1] recently has contributed a valuable paper. Some may be syphilitic; some are doubtless instances of true tumor formation; some are probably a proleukemic or aleukemic stage of true lymphocytic leukemia; while some are what may be called true Hodgkin's disease. Dorothy Reed[2] and Simmons,[3] for instance, contend that pseudoleukemia, or Hodgkin's disease, presents a definite histologic picture, and that it has no direct relationship whatever to leukemia or tuberculosis. Klein[4] quite recently has given a good discussion of lymphocythemia and lymphomatosis.

[1] The Relation of the Tubercle Bacillus to Pseudoleukemia (Sternberg's Disease), Philadelphia Medical Journal, 1902, vol. x. pp. 615, 669.

[2] On the Pathological Changes in Hodgkin's Disease, with Especial Reference to its Relation to Tuberculosis, Johns Hopkins Hospital Reports, 1902, vol. x. p. 133.

[3] Hodgkin's Disease: A Pathological Analysis of Nine Cases, Journal of Medical Research, 1903, vol. ix. p. 378.

[4] Lymphocythämie und Lymphomatose, Zentralblatt für innere Medizin, 1903, vol. xxiv. pp. 817, 849.

Finally, a word with regard to the clinical manifestations of acute lymphocytic leukemia. Its resemblance to scorbutus and to sepsis is well known, but what is of especial interest is the marked resemblance that some cases, particularly those without noteworthy enlargement of the lymph glands, bear to typhoid fever. I believe that there is some reason to think that some cases have been presumed to have been typhoid fever, and even at the necropsy the error has not been rectified. The clinical resemblance in many of the symptoms is striking, the duration is about that of typhoid fever, and the intestinal lesions, the infiltration and ulceration of Peyer's patches, are extremely suggestive of typhoid fever, particularly on superficial examination. The differential diagnosis is determined by the results of an examination of the blood and by a microscopic examination of the tissues after death.

A CLINICAL AND PATHOLOGICAL STUDY OF TWO CASES OF SPLENIC ANEMIA, WITH EARLY AND LATE STAGES OF CIRRHOSIS (EARLY AND LATE STAGES OF BANTI'S DISEASE).

By GEORGE DOCK, M.D.,
OF ANN ARBOR, MICHIGAN,

AND

ALDRED SCOTT WARTHIN, M.D.,
OF ANN ARBOR, MICHIGAN.

(From the Laboratories of Internal Medicine and Pathology, University of Michigan, Ann Arbor.)

INTRODUCTION.

THERE is a growing belief in the existence of a disease described under many names—always a sign of ignorance—but at the present time called splenic anemia more frequently than by any of the other synonyms. The term has been loosely applied, and, in fact, invites loose application, unless one has some acquaintance with the literature of splenic diseases and remembers "the good rule laid down by Socrates," as quoted by Osler. With that precaution, we think with Osler and Senator that splenic anemia is a better word for the purpose than any other yet suggested. Since Banti showed the evolution of certain cases with enlarged spleen and anemia into later stages with ascites and cirrhosis of the liver, his name has been used by some as a synonym, and, although Osler's suggestion that it be applied only to the later stages will doubtless have many followers, it will often be difficult to draw a line; for, though Banti thought he had discovered a disease distinct from splenic anemia, he was aware of the difficulty of making a final conclusion. Even in the more

recent literature, under the names splenic anemia and Banti's disease, we find, besides some obviously faulty diagnoses, certain cases that differ from the generally accepted picture in some details. Senator, in adding greatly to our knowledge, showed that the symptomatology of the blood is not as Banti described it. Since not only this, but also many other allied topics in splenic pathology are only beginning to receive investigation, it is necessary to enlarge the casuistry and to collect and report as many cases as possible in which the clinical and anatomic features have been carefully studied. Banti's suggestion of extirpation of the spleen has already been of great benefit, not only as a therapeutic measure, but by increasing our knowledge of the changes in different stages, and should be followed in well-selected cases.

In the following we report two cases bearing upon the subject. One of these seems a good example of splenic anemia in a comparatively early period. Clinically it is a good example of splenic anemia in the old sense, but anatomically it shows changes in the liver that indicate the occurrence of cirrhosis of the liver had the condition gone on longer. The other has many of the features of Banti's late stage, but is complicated by an old and obscure peritonitis. Since this does not seem to have causal relations with the important changes in the liver and spleen, we report the case on account of the other changes. We do not intend to consider now the literature of the subject, reserving that for another time.

Part I. Clinical (Dr. Dock).

Case I. *Splenomegaly, anemia; removal of spleen; death. Fibrosis of spleen; beginning fibrosis of liver; stenosis and calcification of the portal vein; hyperplasia of hemolymph nodes; new formation of lymphoid tissue.*—I. T. A., aged forty-one years, was admitted to the University Hospital as an out-patient July 27, 1899.

Family History. Father died at seventy-two years, having had a cough for twenty years. Mother died at seventy-eight years of pneumonia. Patient had six sisters and two brothers; two brothers and two sisters are alive. Two sisters died of consumption, one in childbirth, one of "stomach disease." One brother died of "brain disease." Patient has one daughter, aged ten years, in good health. (Though a strong and robust girl, she had extensive pharyngeal adenoids, besides enlarged tonsils, and some months after this underwent operation for appendicitis, when the lymphoid tissue of the appendix was found to show a marked hyperplasia without other signs of

appendicitis.) The patient's wife died one year ago of leukemia. (She was treated as an in-patient and out-patient of the Medical Clinic for a year and a half, during which time the husband showed a great interest in splenic disease, bringing to the hospital several patients supposed to have enlarged spleens.)

Habits and Occupations. Patient lived on a farm in his youth; since the age of twenty-one years has been in mercantile business. Has worked hard and at long hours, but has not suffered from that, and has not been unusually exposed. Meals have been regular; food good. Appetite has always been good, but bowels irregular. Has used little tea and coffee for ten years; alcohol rarely; tobacco not at all.

Previous Diseases. Had the usual diseases of children; had a severe fever, probably typhoid, seventeen years ago, and a mild attack of influenza a few years ago. Had always been subject to sick headache, but in 1901 had rectal "polyps and ulcers" operated (by a notorious "orificial surgeon"), and headaches have been less severe since then. Most careful inquiry could elicit no history of venereal disease.

Present Disease. About a week ago first noticed a soreness in the left hypochondrium and uneasiness in the abdomen, and on feeling discovered a tumor in the left side. He had noticed a gradual enlargement of the abdomen for a year, but thought nothing of it.

Status præsens, July 27, 1899 (Dr. Arneill). Frame of medium size, rather slender muscles; small and soft; panniculus thin; weight, 126 pounds, the usual weight in summer. The bones and joints are normal; the inguinal glands can be felt; the other superficial lymphatic glands are not enlarged.

The gait is normal, appearance somewhat cachectic, expression depressed, mind clear.

The skin is somewhat pale and sallow, the visible mucous membranes of fair color.

The teeth are artificial; the tongue is of medium size; has a thin, white, moist coat.

The thorax is of good size and shape; expansion moderate; percussion and auscultation of lungs negative.

The apex-beat is in the fourth interspace, one inch inside the nipple line; the dulness is not enlarged; the sounds normal; no murmurs.

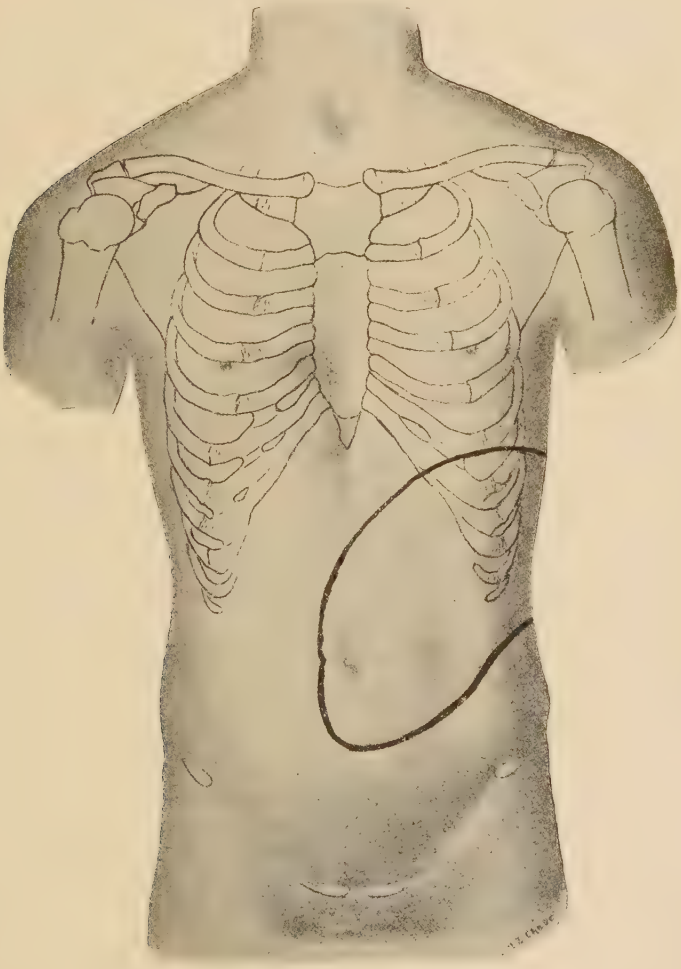
The abdomen is an inch above the level of the ribs, larger in the left side. The liver dulness extends from the sixth interspace to the edge of the ribs; the thin edge can be felt an inch below the ribs in deep inspiration. The splenic dulness begins on the seventh rib, in the mid-axillary line; extends through Traube's space to the navel line in the left nipple line, and two inches below the navel in the middle line. On palpation a hard mass can be felt in this region, having a sharp angle two and a half inches below the navel. A sharp edge runs up one inch to the right of the navel, and shows a notch an inch above the navel.

The radial artery is somewhat tortuous, the pulse easily compressed, mod-

erately full, tension medium, rate 90, regular. The veins of the thorax, especially on the right side and shoulder, are easily seen. The patient says this has always been so.

The urine shows a trace of albumin; no casts; otherwise negative.

FIG. 1.



CASE I.

The blood: Red corpuscles, 4,480,000; leukocytes, 5857; hemoglobin, 75. July 29. Test breakfast shows good digestion and motor power; Congo positive; Günzberg negative.

The patient was ordered Fowler's solution and dilute hydrochloric acid.

August 29. Patient returns for examination, saying he feels better at times. He complains of pain in the right side. The tumor is still present, the boundaries being the same as in the previous examination. Leukocytes, 6366.

September 20. The patient is still sallow and cachectic, the spleen slightly smaller than at the last examination.

Examination of the stained blood taken at the early visits had shown red corpuscles of fairly uniform size, a few normoblasts, no megaloblasts or myelocytes. Returning from my vacation, I examined the specimens that had been preserved with great interest. Finding nothing essentially different from what is noted above, I sent for the patient, found the history and physical condition accurately described, and made further examinations of the blood.

22*d*. Differential count (Dr. Dock). Small lymphocytes, 32 per cent; large lymphocytes, 5 per cent.; large mononuclear and transitional, 6 per cent.; polymorphonuclear, 52 per cent.; eosinophiles, 4 per cent.; degenerates, 1 per cent.; normoblasts, 4 to 100 leukocytes. The red corpuscles vary considerably in size and shape, but there are no very large or very small cells. Many cells show vacuoles. There are no polychromatophiles. The normoblasts have the usual characters well marked. Only one shows irregular staining of the nucleus. The polymorphonuclear leukocytes show a good many large ones, with small, deeply-staining nuclei. The lymphocytes are mostly very small, the nuclei staining deeply and showing fragmentation The eosinophile cells are all of normal appearance.

The general appearance of the blood resembled that often seen in pernicious anemia at times of comparatively good health. Numerous examinations showed a total absence of megaloblasts and of Ehrlich's myelocytes, as well as of any other indication of bone-marrow disease. The diagnosis of leukemia in the aleukemic stage, such as the patient's wife had at one time, was ruled out, and as the result of a differential diagnosis not necessary to detail here, splenic anemia was accepted. In view of the theory of Banti and of the operations based on it or a similar theory, I advised an attempt at removal of the spleen, which, after some consideration, the patient accepted. The advice was given on October 2d, but as the patient wished to arrange his affairs before the operation, he was examined at long intervals in the next month. In this period there was an interesting change in the proportion of the various forms of leukocytes, as appears best from the following counts, which include all up to the last day:

29*th*. Hemoglobin, 60; red blood corpuscles, 3,640,000; leukocytes, 2037; normoblasts, 1 per cent.; small lymphocytes, 22.5 per cent.; large lymphocytes, 3.6 per cent.; transitionals, 1.5 per cent.; polymorphonuclears, 60.1 per cent.; eosinophiles, 5 per cent.; degenerates, 7.3 per cent.

October 2*d*. Hemoglobin, 70; red blood corpuscles, 4,288,000; leukocytes, 2546; normoblasts, 1 per cent.; small lymphocytes, 25 per cent.; large

lymphocytes, 3 per cent.; transitionals, 3 per cent.; polymorphonuclears, 63 per cent.; eosinophiles, 3 per cent.

15*th*. Normoblasts, 1 per cent; small lymphocytes, 15.5 per cent.; large lymphocytes, 5 per cent.; transitionals, 1 per cent.; polymorphonuclears, 75.5 per cent.; eosinophiles, 3 per cent.

November 1*st*. Hemoglobin, 75; red blood corpuscles, 4,300,000; normoblasts, 0.9 per cent.; small lymphocytes; 18 per cent.; transitionals, 7.4 per cent.; polymorphonuclears, 78 per cent.; eosinophiles, 3.5 per cent.

3*d*. Normoblasts, 1.1 per cent.; small lymphocytes, 8.6 per cent.; large lymphocytes, 13.2 per cent.; polymorphonuclears, 76 per cent.; eosinophiles, 2.6 per cent.

4*th*. Leukocytes, 3056; normoblasts, 1 per cent.; small lymphocytes, 6 per cent.; large lymphocytes, 4.33 per cent.; transitionals, 2.66 per cent.; polymorphonuclears, 85.66 per cent.; eosinophiles, 1.33 per cent.

6*th*. During anesthesia, leukocytes, 4909; small lymphocytes, 6 per cent.; large lymphocytes, 4 per cent.; transitionals, 4 per cent.; polymorphonuclears, 84.5 per cent.; eosinophiles, 1.5 per cent.

7*th*. Leukocytes, 18,080; normoblasts, 4 per cent.; large lymphocytes, 1.5 per cent.; transitionals, 4.6 per cent.; polymorphonuclears, 91.9 per cent.; degenerates, 1.9 per cent.

9*th*. Leukocytes, 21,000; normoblasts, 6 per cent.; large lymphocytes, 2.9 per cent.; transitionals, 4.6 per cent.; polymorphonuclears, 90.8 per cent.; degenerates, 1.4 per cent.

Not only were the small lymphocytes less numerous, but the most typical forms were even fewer than the figures indicated, because the small and large lymphocytes showed many intermediate forms. The nuclei stained less intensely, but clearly, resembling those of large lymphocytes. Degenerated leukocytes were usually numerous up to the time of operating, and were nearly all of the polymorphonuclear class. These cells, therefore, were more numerous than in the beginning of the observation, but showed an unusual tendency to break down. While they are largely artefacts as found in the preparations, the variable numbers are suggestive.

October 31*st*. Patient enters hospital. Appetite is good; general condition as before.

November 3*d*. The spleen extends from one and a half to two inches below the navel, in the middle and left parasternal lines. There is a palpable groove half an inch above the navel.

6*th*. The spleen was removed under ether anesthesia by Dr. C. B. Nancrede. There was considerable distention of the intestines. The spleen had very few adhesions at the anterior surface, but there were many at the upper end. The upper end was unusually thick in proportion to the other dimensions, and this, with the adhesions and the great size of the vessels, made the removal unusually difficult. Slight symptoms of shock appeared as the vessels were being tied. The pulse and respiration were good all through, but perspiration became profuse just at the end. After the

operation there was marked tympanites, frequent and small pulse; the mind was clear. The patient, who had before looked on the operation with calmness, became very [illegible] and on November 9th, three days after the operation, became collapsed, with cold skin, sweating, pallor, small and soft pulse of 88 beats to the minute and died on November 10th, at 3.30 P.M.

CASE II. *Interstitial hepatitis with Glisson's cirrhosis; ascites; splenomegaly; fibroid tumors of uterus; hypertrophy; removal of fibroids; discovery of cirrhosis of liver at operation; death from hemorrhage from varicose vein in stomach; sclerosis and calcification of portal vein; fibrosis of spleen and liver (atrophic cirrhosis); hyperplasia of lymph nodes.*—Mrs. M. S., aged fifty-three years, housewife, born in Michigan, was admitted to the Medical Clinic of the University Hospital October 7, 1902. She had entered the Surgical Clinic for treatment of hernia, but was referred to the Internal Clinic on account of ascites.

Family History. Mother died at age of fifty-eight years, of "consumption." Father died at seventy-two of "heart disease." Four brothers and four sisters are in good health. Habits and mode of life have been good.

Previous History. Patient had whooping-cough, measles and mumps in childhood, with good recoveries. Menstruation began at fourteen, stopped for a year, and was regular after that, lasting about three to four days, without unusual symptoms. At thirteen had an attack of "dysentery," in which she passed much blood. At nineteen was married. Has never been pregnant. (No reason for this could be discovered.) Syphilis seems positively excluded. Menopause in fiftieth year.

Six years ago the patient had "dysentery" and was confined to bed for six weeks. She passed large amounts of blood with loose and watery stools. Since then she has had similar attacks at intervals. A week before admission had a slight diarrhea, without blood in the stools. After the attack six years ago the abdomen gradually became larger, and at that time Dr. H. A. Shurtleff, of Pontiac, Mich., discovered free fluid in the abdomen, by physical signs. Soon after that edema of the legs and ankles came on, lasting for two months. It has recurred at intervals since then, but less severely. The umbilical hernia appeared after vomiting, three years ago, and has grown larger: the inguinal hernia came on after coughing, one and a half years ago.

The patient now complains of constant soreness over the whole abdomen. She is constipated and has frequent desire to defecate, but bowels are moved with difficulty. Appetite fair, but patient eats sparingly on account of feeling of distension and sensation of weight in abdomen.

Status praesens. October 7, 1902. Medium height, slender frame; muscles small and soft; panniculus scanty; weighs 120 pounds; best weight, ten years ago, 150. The joints are normal, reflexes not altered, superficial lymphatic glands not enlarged.

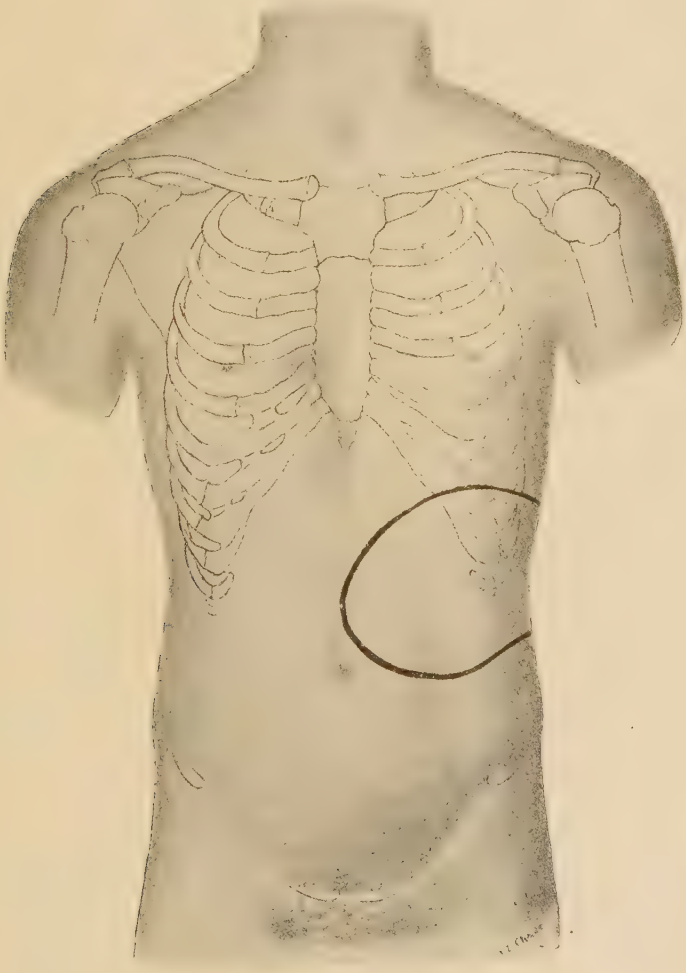
The patient looks weak and cachectic, the expression is weary; mind clear.

The skin is pale, sallow, and inelastic; the visible mucous membrane pale; there is no edema.

The teeth are artificial; the tongue is white-coated.

The thorax is broad, short, wide; epigastric angle wide and lower aperture of thorax distended. The expansion is fairly good, and symmetrical. The

FIG. 2.



CASE II.

right lower lung border is on the sixth rib, the descent limited. Percussion of lung, front and back, negative. Auscultation reveals good vesicular murmur.

Heart. The apex-beat is indistinct, but can be felt in the fourth interspace, just inside the nipple line There is a faint pulsation in the third left interspace. Cardiac dulness begins on the third rib, extends to within half an inch of the nipple line. Dulness under the sternum from the fourth rib down, to the right of the sternum in the fifth interspace, one finger's breadth. The apex sounds are clear, the first accentuated. In the pulmonary area there is a short systolic murmur, followed by an accentuated second sound, lower than the aortic second. Radial pulse slightly tortuous, perhaps slightly thickened; rhythm regular, tension low.

The abdomen is enlarged, measuring thirty-seven inches at the umbilicus. It is bulging at the sides and flattened on top, with a prominence in the umbilical region. (During the examination this prominence subsided, leaving a slight depression in the same place.) The superficial abdominal veins are not enlarged. There are a few large venules over the anterior spines of the iliac bones. In the left side, above and below the iliac crest, some small veins are visible through the skin. On sitting up the protrusion reappears in the umbilical region, becoming larger than before. There is also a wide separation of the recti, permitting a great protrusion all the length of the abdomen. A large hernia also appears in the right inguinal region. The intestines can be plainly felt through the skin in the middle part.

Lying down, there is dulness on percussion in both flanks, almost to the nipple lines, and in front two inches above the pubes. The lines change quickly on change of position. Fluctuation is not distinct. Palpation of the lower abdomen is negative.

The liver dulness reaches to the margin of the ribs in the nipple line. Palpation is unsatisfactory on account of the distention.

Splenic dulness begins at the seventh rib, and is continuous with the dulness in the flank. The lower end can be felt about three inches below the edge of the rib.

Examination of the anus and rectum shows the small atrophic tags of old external hemorrhoids, and very small internal hemorrhoids, without evidence of hemorrhage. The mucosa shows a bleeding spot the size of a pin-head about six inches from the sphincter.

Examination of the pelvic organs (Dr. Peterson.) Negative.

Examination of urine. Negative.

The blood flows freely; is thin; bright red. Red blood corpuscles, 2,800,000; leukocytes, 5857; hemoglobin, 60 per cent. The differential count gave: small lymphocytes, 6 per cent.; large lymphocytes, 5.9 per cent.; large mononuclears and transitionals, 4.2 per cent.; polymorphonuclears, 81.7 per cent.; eosinophiles, 1.2 per cent.; degenerates, 0.6 per cent.; normoblasts, 3 per mille. The red corpuscles show very slight variation in size and shape.

October 21. The superficial veins of the abdomen are slightly distended. Abdomen tapped in Monro's point and 3800 c.c. of fluid withdrawn. The fluid is clear, reddish-yellow, specific gravity, 1012. It contains a slight in-

crease of red blood corpuscles. Differential count of the other cells: small lymphocytes, 53 per cent.; large lymphocytes, 8 per cent.; polymorphonuclears, 6 per cent.; large mononuclears, 33 per cent. The large mononuclear cells have the appearance of young endothelial cells; the lymphocytes partly that of endothelial cells, partly that of ordinary lymphocytes.

After tapping, the abdomen measures thirty-two and three-quarter inches at the umbilicus. The spleen can be easily felt three fingers' breadth below the ribs, and reaching to the median line. Liver dulness not quite to edge of ribs. Liver cannot be felt.

22*d*. Patient has been more comfortable since the tapping. There is gaseous distention in the right side. The spleen reaches the navel line in the nipple line and the middle line, four fingers' breadth above the umbilicus. The surface of the spleen is smooth, flat; the edge thick; there is a notch above the lower end, on the inner side.

24*th*. The abdomen is larger; thirty-four and a half inches. Signs of free fluid not so extensive as before the tapping. The ankles are slightly edematous. The superficial abdominal veins are not enlarged. No murmur in the epigastric region.

Blood. Red corpuscles, 4,266,666; leukocytes, 7894; hemoglobin, 70 per cent. Differential count: small lymphocytes, 3.4 per cent.; large lymphocytes, 6.4 per cent.; transitionals, 11.4 per cent.; polymorphonuclears, 77 per cent.; eosinophiles, 1 per cent.; degenerates, 0.8 per cent. No nucleated red cells found; a few poikilocytes.

30*th*. The patient has complained much of pain and soreness in the pelvis, which could not be explained by any of the manipulations practised upon her. Another consultation was held with Dr. Peterson, and an examination made under ether. A small, hard mass was found in front of the uterus, apparently a fibroid tumor.

Up to this time the diagnosis had not been sufficiently clear to offer a surgical operation to the patient, who was convinced that medicines would not relieve her. Cirrhosis of the liver, most likely at first glance, was made doubtful on account of the history, the long duration of ascites without more venous enlargement, and the relatively large spleen. A Talma operation did not seem warranted. A late stage of Banti's disease seemed ruled out also by the long duration of the ascites and relatively good condition of the blood. On the other hand, I presented the patient both in clinic and before the Medical Society as a possible case of late Banti, with a complication, perhaps in the pelvis, causing chronic peritonitis, and with the blood picture (polymorphonuclears increased relatively) obscured by the local conditions in the abdomen. Here, too, surgical intervention did not seem more promising than it did on the theory of cirrhosis, because if the case was one of Banti's it was probably past the aid of surgery; and my surgical colleague declined to explore in order to determine that point. Tuberculosis and malignant disease of the peritoneum were ruled out by the long duration and the character of the fluid, as well as other features not necessary to point out.

Chronic peritonitis due to an undiscovered disease in the pelvis was a diagnosis I took up several times to explain the ascites as an associated phenomenon with the enlarged spleen, but up to the discovery of the fibroid this diagnosis did not lead to an exploration.

Although the fibroid could not be correlated with the enlarged spleen, or even the ascites, save as an exceptional condition, it gave us something to operate for, and so meet the pressing wishes of the patient as well as our own desires for an exploration. Accordingly, Dr. Peterson operated November 7th. A large amount of fluid having the same character as that previously examined escaped from the incision. An irregular, roundish tumor, one and a half inches in diameter, was found adherent to the lower and anterior part of the uterus. It proved to be a calcified fibromyoma. The uterus was very small, the fundus round and of stony hardness. It was found to be merely a shell around another calcified fibroid, and was removed. There was no distinct disease of the tubes and ovaries, but there were many adhesions around all the pelvic organs. The omentum was fastened low down by adhesions. The spleen was large, the lower surface uneven. The liver was also uneven to the touch, though as seen by light thrown into the abdominal cavity it showed only slight granular change. There were numerous adhesions around the liver and spleen.

The wound healed well at first, but left a small sinus. The ascites gradually returned, and on December 2 five liters of fluid were removed. Specific gravity, 1012

December 6th. The patient returned to the medical ward. *Status præsens.* The patient looks tired and sleepy, and complains of feeling sick all over. She has had diarrhea, with great pain. The stools were dark and watery, and contained fresh blood. The abdomen measures thirty-four inches. The abdominal veins are distinct but not swollen. Palpation of the abdomen causes pain. The wall is soft in general. There is a flattened mass just above the navel line and two inches to the left of the navel, apparently adherent to the deep tissues. The spleen extends not quite two fingers' breadth below the ribs in the nipple line, three fingers' breadth in the parasternal line. There is a soft blowing systolic murmur over the base of the heart. A few crackling râles can be heard in the right axilla.

There had been leukocytosis even since the operation, from 10,000 to 18,000 per cm., with increased percentage of polymorphonuclear cells and many degenerates.

Red blood corpuscles, 3,040,000; leukocytes, 17,200; hemoglobin, 40 per cent. Differential account: small lymphocytes, 12 2 per cent.; large lymphocytes, 2.2 per cent.; transitionals, 1.1 per cent.; polymorphonuclear, 84 per cent.; eosinophiles, 0.45 per cent. No nucleated reds. Moderate poikilocytosis.

At 1.45 P.M. the patient vomited half a pint of blood, and twenty minutes later a similar quantity. The blood is bright red, alkaline; contains large clots. At 6.30 P.M. patient vomited about six ounces of bloody

fluid. Pulse small and irregular. Patient feels weak, dizzy, and nauseated.

7th. Patient feels better. Has not vomited, but passed bloody fluid per rectum.

8th. Patient is weaker and in great pain. Retention of urine.

9th. Still passing bloody fluid per rectum. Cannot swallow.

10th. Incontinence of rectum.

11th. Died at 12.05 P.M.

Part II. Pathology (Dr. Warthin).

Case I.—Mr. I. A., aged forty-one years, American. Died November 10, 1899, at 3.30 P.M. Autopsy by Dr. Warthin, 7.30 P.M., November 10, 1899.

Autopsy Protocol. Body of average height and build. No anomalies or deformities. No signs of trauma. In the left hypochondrium there is a recent laparotomy wound, extending from the edge of the ribs to within three fingers' breadth above the iliac crest. It is covered with surgical dressings. On removing these the edges of the wound are found to be separated and a fold of intestine protruding. Edges of the wound are discolored (gray to black), but present no evidences of pus. Abdomen distended above the level of the ribs.

The skin is pale, sallow; there is slight hypostasis posteriorly; small boil on right forearm; teeth artificial; hair is negative. The panniculus is greatly decreased; no edema; muscles are small and emaciated; rigor mortis is present throughout. The extremities are cold. There are no signs of decomposition.

Brain and *spinal cord* not examined. (No permission.)

Diaphragm at the fourth rib on the right; fifth rib on the left.

Position of thoracic organs is normal. Apex of heart in fourth intercostal space, just inside of the nipple line. The mediastinum is rich in fat; no enlarged glands. The thymus fat is in large amount, and in it there is found a pinkish lobulated body 3 cm. long by 1 cm. in diameter. There is no fluid in the pleural cavity. Both pleuræ are free; there are no adhesions.

The *pericardium* is lax; contains a very small amount of clear fluid. Subepicardial fat is slightly increased.

Heart weighs 320 grams; is about the size of cadaver's right fist. The auricles contain ante-mortem white clots; the ventricles are filled with fluid blood and currant-jelly clot. The heart muscle is firm, brownish-red; papillary muscles are prominent. The left ventricle wall measures 15 to 20 mm. in thickness. The endocardium is slightly thickened. The pulmonary, tricuspid, and aortic artifices and valves are normal. The mitral orifice is rather small; does not admit two fingers. Mitral flaps are slightly thickened and shortened. Coronary vessels are negative.

Right lung weighs 272 grams; *left lung* weighs 336 grams. Both lungs are partly collapsed. Pleuræ negative. Slight anthracosis. On section the

parenchyma of lungs is grayish-pink; lower lobes slightly hypostatic; no airless areas; very slight exudate on pressure; bronchi are empty; mucosa pale; pulmonary vessels negative; bronchial glands moderately pigmented; on section negative. A number of enlarged glands along the thoracic aorta. On section they are red and spleen-like. The great vessels of the thorax and the thoracic duct are negative.

Mouth and *neck organs* were not examined.

Abdomen. The omentum is rolled up, greatly thickened, and moderately injected, and is adherent to the diaphraghm and anterior abdominal wall in the splenic region, and to the peritoneal surface of the ileum by fresh fibrinous exudate. In the region of the spleen there is a large mass of fresh fibrinous adhesions, but no evidence of hemorrhage. Spleen (see below) is absent, having been removed at operation. Ligatures on stumps of splenic vessels are in position. Splenic vessel filled with fresh red thrombi.

The small intestine is greatly distended throughout. The serosa is cloudy, moderately injected, and everywhere covered with a fine fibrinous deposit. Many of the coils are adherent by coarser strings of fibrin, the adhesions being easily separated. The lower sixteen inches of the ileum lie in the left side of the abdomen, a portion of the ileum projecting through the laparotomy wound. Coils of the ileum are adherent to each other by fibrinous exudate, the adhesions being firmer in neighborhood of wound. They are also adherent to the large intestine by a similar fresh fibrinous exudate. About two and a half inches above the cecum there are several (six) dark patches in the intestinal serosa, covered with greenish-gray fibrin. These patches are irregular, not triangular in shape, and do not extend entirely around the bowel; some reach about two-thirds of the way. From the serosa these patches extend some little distance into the fat of the mesentery, which shows a superficial necrosis corresponding to the patches of fibrin. These areas have the appearance of having been cauterized; they are all on the upper surface of the mesentery.

The *stomach* is greatly distended, its wall very thin. It lies pressed against the anterior abdominal wall, and was cut during the median incision, letting out a large quantity of sour-smelling gas under high pressure. It contains about 500 c.c. of brown, bile-stained, sour fluid. The mucosa of the stomach shows slight postmortem change. Veins of stomach wall are greatly distended. The large venous branches in the greater curvature contain fresh thrombi. Around the gastroepiploica sinistra there is a ligature which includes the serosa of the stomach wall, but not the muscle coats. The coronary veins are greatly dilated, as are also the anastomoses with the esophageal veins.

The *duodenum* is greatly distended with gas; it contains a small amount of grayish, slimy material. Its mucosa is injected and somewhat swollen. Bile passages are patent.

The *ascending* and *transverse colon* and *cecum* are greatly distended as far as the splenic flexure, the descending colon being more moderately distended.

They contain a small amount of formed feces and a large amount of grayish mucus. The sigmoid flexure and the descending colon are unusually pale and nearly white. The *appendix* is long and narrow, extends into pelvis; no adhesions about it.

Liver weighs 1280 grams, measures 23 x 15½ x 8 cms; is small; left lobe very atrophic; right lobe shows posteriorly a number of small anomalous lobules. Capsule is thickened, especially near the ligaments. Veins of capsule congested. Small cavernous angioma, size of a pea, on the upper surface of the right lobe. On section the blood-content is found to be fairly rich. In one of the larger branches of the portal there is a fresh but firm red thrombus. The cut surface of the organ is granular, in some areas markedly so; the granules slightly elevated. The largest granules are paler in color than the remainder of the liver parenchyma, which is of a pale brown color. Outlines of the lobules are distinct over the greater part of the cut surface; they are smaller than normal. The peripheral zone of the lobules is more grayish, cloudy, and apparently swollen. The connective tissue is apparently increased. In some areas the tissue of Glisson's capsule is thickened, hyaline, and scar-like. In about the middle of the right lobe there is an area about 5 cm. in diameter, which is firmer and lighter in color than the other portions of the cut surface, and is slightly elevated and more distinctly granular. In this area the connective tissue seems to be increased to a greater extent, and the lobules are larger than elsewhere.

The *gall-bladder* is distended, containing about 200 c.c. of dark brown fluid and three grayish cholesterin stones of small size. Its mucosa is very thin, the wall much stretched.

The *portal vein* is extremely distended, and is filled with a fresh but firm mixed clot. The lumen of the vein at its beginning, just above the union of the splenic and superior mesenteric veins, is irregularly narrowed and partly bridged off by fibrous valve-like constrictions which contain calcareous plates. The vein is divided by these fibrous bands into several sac-like spaces, the walls of all these showing calcification. The tortuous lumen barely admits the tip of a lead-pencil or large probe. The stenosis involves the mouth of the splenic vein, almost completely occluding it. The splenic and superior mesenteric veins back of the stenosis are enormously distended and filled with a soft red thrombus, which is continuous with the firmer mixed thrombus filling the portal. In the media of the portal vein at the point of constriction there are thin plates of calcification. The walls of the splenic and mesentery veins are greatly thickened, and present scattered patches of hyalin.

The *pancreas* is of normal size; on section apparently normal, save for congestion and small areas of hemorrhage. The splenic vein and its pancreatic branches are greatly distended and are filled with firm red thrombi. In the neighborhood of the pancreas there are several glands resembling accessory spleens. They possess very thick capsules.

In the root of the mesentery, particularly near the portion of ileum show-

ing the dark fibrin patches, the lymph glands are slightly enlarged and hyperemic. Hyperemic patches are scattered over the surface of the mesentery, in some cases grayish-black; these are covered with fibrinous exudate.

The *retroperitoneal lymph glands* are not enlarged, but are red, firm, and spleen-like. Abdominal aorta, iliacs, etc., negative.

Ureters negative.

Bladder empty, collapsed; mucosa pale.

Adrenals show postmortem softening of medullary portion.

Kidneys. The fatty capsule of both kidneys is moderately rich in fat; the fibrous capsule strips easily and is not thickened. The right kidney measures $9\frac{1}{2} \times 5 \times 3\frac{1}{2}$ cm., and weighs 128 grams. The left kidney measures $10\frac{1}{2} \times 4\frac{1}{2} \times 3$ cm., and weighs 112 grams. The surfaces of both kidneys are bright red, and the venæ stellatæ well marked. On section both kidneys are bright red. Cortex of each measures $\frac{1}{2}$ to $\frac{3}{4}$ cm. Outlines between labyrinths and medullary rays not well defined; glomeruli not visible; consistence firm; bloodvessels engorged; pelvis of left kidney somewhat dilated, that of right negative.

Ureters and *bladder* negative.

Genitals. External genitals negative. Testicles and epididymes negative. Prostate and seminal vesicles not examined.

Aorta, iliacs, iliac veins, femorals, and *vena cava* negative.

Bones. Negative. Right tibia, fourth lumbar vertebra, and several ribs removed. Tibia split longitudinally. Slight hyperplasia of red marrow. Small lymphoid areas throughout the fatty marrow; the largest of these, in the middle of the tibia, measures $\frac{1}{2} \times \frac{1}{4}$ cm.

Peripheral Glands, Nerves, and Vessels. Negative. (Material was taken from all parts and organs of the body, fixed in Flemming's solution, Müller's, mercuric chloride, alcohol and formalin, and embedded in celloidin and paraffin, and stained by ordinary and special staining methods.)

Microscopic. Heart. Sections show atrophy of heart muscle and slight increase of connective tissue.

Lungs. Sections taken from different portions show a number of small recent and old hemorrhagic infarcts. Many of the alveolar walls are thickened, and there is an increase of connective tissue about the larger vessels. In the lower lobes there is slight emphysema. The bloodvessels are congested, and many of the smaller arteries show sclerotic changes. A few organizing thrombi are formed. Anthracosis is moderate. There is a slight edema. In the capillaries there are found numerous emboli of bone-marrow giant cells, similar to those found in the spleen and liver. These are so numerous that three to six may be found in one field. In the small arterioles the protoplasm of the giant cell is preserved, in the capillaries only the deeply-staining knobbed and lobulated nuclei are visible. A few multinuclear giant cells are found in the arterioles.

Liver. In the sections taken from all parts of the liver, with the exception of the elevated area in the middle of the right lobe, the lobules are atrophic,

the atrophy involving chiefly the central portions of the lobules. The central veins and capillaries are dilated, while the liver cells of the central zone are atrophic or in part necrotic, or show varying stages of fatty degeneration, cloudy swelling, and necrosis. In some lobules the liver cells of the central zone have completely disappeared. In the majority of lobules there is an endothelial or fibroblastic proliferation in the capillaries of the central zone. This is most marked in those areas showing the most pronounced atrophy or necrosis of the liver cells. The liver-rods present a more decided radiating appearance than usual, and in many places appear as if elongated by pressure. The periportal islands of connective tissue are relatively increased in number; the connective tissue in the majority being of a hyaline character and presenting no infiltration. The fine reticulum of the lobules is everywhere increased, but particularly in the areas of most marked atrophy, where it replaces in part the liver cells. In many areas it is very cellular and presents an endothelial or fibroblastic proliferation. With Van Gieson's stain the greater part of the newly formed reticulum stains a light red. By the same stain heavier lines and strands of connective tissue may be seen in places extending into the lobule. Small focal necroses are found scattered throughout the sections; the necrotic areas showing the same endothelial or fibroblastic hyperplasia as seen in the central part of the lobules. Hypertrophic liver cells are also found throughout the lobules. The central veins and branches of the hepatic veins are greatly dilated and their walls thickened. Giant cells are found in the capillaries; they resemble bone-marrow giant cells and are similar to those found in the lungs and spleen, but are not nearly so numerous as in those organs. In many sections the only changes are those of a chronic passive congestion.

Sections taken from the yellowish, elevated area in the middle of the right lobe show that the liver-lobules are larger and the liver cells are increased in size, the blood capillaries being nearly obliterated. Many of the liver-cell nuclei are very large and stain deeply. In Glisson's capsule there is a marked small-celled infiltration and proliferation of the connective tissue and the smaller bile-ducts. The periportal connective tissue is somewhat increased and the finer reticulum of the lobule likewise shows an increase. The central congestion and atrophy is less marked in this portion.

The liver as a whole presents the picture of a chronic passive congestion and atrophy of the central portions of the lobule, with an increase of the reticulum of the lobules, chiefly central, but also periportal. This increase is in many places due to a fibroblastic proliferation. In some areas these changes are so marked as to warrant their interpretation as a beginning stage of cirrhosis, in part central and in part periportal.

Portal Vein. Sections of the wall show sclerotic changes and calcification, involving chiefly the media. No evidence of recent phlebitis. Branches of portal show similar conditions. Fresh thrombi in all branches.

Stomach and intestines present the picture of a chronic passive congestion with atrophy and chronic catarrhal inflammation.

Pancreas shows decrease in size of lobules and a moderate fatty infiltration. Near the middle of the body of organ a small adenoma size of a pea was found. This consists of tubules lined with simple columnar cells, the majority showing mucoid degeneration. Pancreatic veins greatly dilated, and walls thickened.

Omentum. Congested and edematous, and showing a marked small-celled infiltration and fibroblastic proliferation, hemorrhage, etc. Surface covered with a fibrinous exudate.

Mesentery. Peritoneal surface shows patches of fibrin. Very slight small-celled infiltration near surface. The necrosed patches on upper surface correspond to small areas of anemic necrosis caused by the thrombosis of small mesenteric vessels. Mesenteric veins greatly dilated and sclerotic. Throughout the root of the mesentery are small calcareous nodules surrounded by areas of lymphoid cells. Other collections of lymphoid cells surround small concentric hyaline masses, others surround small arterioles showing hyaline thickening of the intima, sometimes arranged in concentric laminæ. As all stages of transition can be found between the calcareous and hyaline nodules and the hyaline vessels, with proliferating endothelium, it seems probable that the former represent a latter stage of the process. The cells surrounding the masses are of the character of lymphocytes, they lie in a fine reticulum containing small bloodvessels, and some contain typical germ-centres. They are, therefore, regarded as representing newly formed lymphoid tissue. Similar formations are found throughout the retroperitoneal fat.

Mesenteric Glands. Atrophic, and contain hyaline areas, some of which show calcification. Vessels congested. Stroma increased. Few germ-centres seen. Numerous phagocytes in sinuses.

Kidneys. Somewhat contracted, the number of glomeruli in a field being greatly increased. Many hyaline and calcified glomeruli are found, as well as numerous cystic ones. Connective tissue stroma increased in areas. Many of the tubules contain hyaline casts. Bloodvessels congested. No giant-cells found in kidney capillaries.

Retroperitoneal Glands. The red spleen-like glands on section are hemolymph nodes, closely corresponding in structure to that of the normal spleen, and are of the type known as hemal glands, possessing no lymph-vessels or sinuses. They are surrounded by a very thick capsule from which trabeculæ containing unstriped muscle run into the gland. No definite blood sinuses are present; the greater part of the gland-structure consists of a pulp like reticulum and blood spaces lined by endothelium. Lymphoid cells lie in the meshes of the reticulum. Small scattered collections of lymphoid cells suggest follicles or germ-centres, but these lack the true vascular relations of splenic follicles. The blood spaces are filled with blood, and occasionally bone-marrow giant cells are found. An unusual number of pigment-containing phagocytes are present in the larger blood spaces. With Mallory's reticulum stain the reticulum appears as a rather coarse, deeply-blue network inclosing spaces filled with blood. The resemblance to normal spleen

is so close that the glands no doubt would be classed as accessory spleens. They resemble very closely the spleen-like hemolymph glands of the hog. The ordinary lymphatic glands of this region are atrophic, present a great increase of reticulum with atrophy of lymphoid tissue and almost complete absence of germ-centres. The lymph sinuses are filled with endothelial cells, many of which contain blood pigment. Cords of newly formed lymphoid tissue corresponding to those in the mesentery lie throughout the retroperitoneal fat. The hemolymph nodes that contain both blood and lymphatic systems do not show the spleen-like hyperplasia seen in the pure hemal glands.

Mediastinal and Cervical Glands. These are atrophic, congested, and are more or less anthracosed.

Bone-marrow. The red marrow is of a lymphoid type, contains an increased number of normoblasts, and very few giant cells. Numerous phagocytes containing blood pigment are present.

Spleen. (Removed at operation by Dr. Nancrede, November 6, 1899.) Nearly a perfect oval in shape. It measures 23 x 13 x 9 cms., and weighs 1536 grams. Its capsule is greatly thickened and covered with fine stringy adhesions which are more numerous in the region of the hilum. The enlargement of the organ is most marked in the upper two-thirds, the thickness diminishing below. On the anterior margin there are two notches at the lower third, the lower one of these extending almost through the lower part of the organ and forming a shelf-like depression. In the hilum there is a small accessory spleen. On section the spleen bleeds freely. The pulp is a pale red and of firm consistence. The stroma is greatly increased. Splenic follicles cannot be seen. On exposure to the air no Charcot-Leyden crystals were formed on the surface.

The organ was received warm from the surgeon's hands. Portions were fixed at once in Flemming's solution, Müller's, mercuric chloride, alcohol, and formalin.

Microscopic. The capsule is greatly thickened, consisting of a rather dense hyaline connective tissue. It is covered with partially or wholly organized deposits of fibrin. The trabeculæ are thickened to a less extent and are much farther apart than normally. The lymphoid tissue of the pulp is scanty, the pulp being replaced largely by a dense fibrous network inclosing the enlarged blood spaces. These are lined and in many cases partly filled by large endothelial or reticular cells having one or more lightly staining nuclei, and in the majority of cases nucleoli. The fibrous tissue represents a hyperplasia of the reticulum of the pulp, the endothelial cells lining the blood spaces apparently taking part in the formation of the new fibrous tissue. In many places, particularly beneath the capsule, it is more dense and hyaline, and the blood spaces are smaller. In the denser areas the fibrous tissue stains deep red with Van Gieson's. In such areas the lymphocytes are very scanty and the endothelial cells are not so numerous. In other portions of the pulp the fibrous tissue is less dense, more cellular,

stains lighter with Van Gieson's, and presents a more fibroblastic character. In such areas the blood spaces are much enlarged and the number of lymphocytes and endothelial cells much greater. The latter are found not only in the spaces, but also between the fibrillæ of the new connective tissue. Occasional giant cells resembling those of the bone-marrow are found in the blood spaces; they are similar to those found in the lungs and liver, and are probably to be regarded as emboli. There is no evidence of their origin *in situ*. Occasional nucleated red blood cells are found in the blood of the pulp spaces, but neither the ordinary stains nor the triacid stain, etc., show any peculiar cells, myelocytes, or other bone-marrow elements to be present. In the neighborhood of the trabeculæ there are found occasional small collections of densely packed lymphoid cells resembling follicles. A thickened hyaline arteriole may be seen in the central portion of some of these collections of cells; others surround small hyaline masses. The blood vessels of the organ are very prominent, being greatly dilated and showing marked thickening of the walls. Small deposits of blood pigment (hemosiderin) are found about some of the trabeculæ, and throughout the pulp spaces occasional endothelial phagocytes containing pigment are seen.

The study of many sections taken from different parts of the spleen leads to the conclusion that the conditions here represent a chronic passive congestion, with great enlargement of the pulp spaces, a coincident or secondary fibrous hyperplasia of the pulp reticulum dependent upon or associated with a hyperplasia of the reticular or endothelial cells lining the spaces. In connection with these changes there is a secondary atrophy of the lymphoid tissue of the pulp and of the follicles. As a result of such atrophy and destruction of the splenic parenchyma the splenic function of hemolysis is gradually lost. The spleen-like hyperplasia of the hemal glands, the new formation of lymphoid tissue throughout the root of the mesentery, and the retroperitoneal fat are regarded as compensatory in character.

Summary of Pathology. The most striking feature of the case is the marked fibrous hyperplasia of the spleen. That this cannot be secondary to the liver condition is shown by the marked differences in degree and character of the hepatic and splenic conditions respectively. The splenic condition is, without doubt, much the older condition, as seen by the greater abundance of the fibrous tissue, its greater density and more hyaline character, and its difference in reaction in areas to Van Gieson's stain; moreover, the atrophic condition of the splenic parenchyma is more marked than that of the liver. The process in the liver is interpreted as a chronic passive congestion and atrophy, followed, secondarily, by an increase of the finer reticulum of the lobules. In several areas, notably in the middle of the right lobe, there is also a beginning periportal increase

of connective tissue with hyperplasia of the smaller bile-ducts. This beginning hyperplasia may be regarded as a very early stage or beginning of a cirrhosis, and is evidently of much more recent occurrence than the splenic condition.

In explanation of the congestion and fibrosis of the spleen, the stenosis and calcification of the portal vein may be regarded as an etiologic factor. That the changes in the wall of the vein at the junction of the splenic and superior mesenteric veins represent an old and not a recent process is shown by the hyaline thickening of the wall and of the fibrous septa and the plates of calcification. These changes must be taken as evidences of an old thrombosis and pylephlebitis, with subsequent organization, contraction, stenosis, and calcification. It is possible that the stasis in the splenic vein and the damming back of the blood upon the spleen have caused the atrophy and the progressive fibrosis seen in that organ. On the other hand, it is also possible that the splenic condition is primary, and the condition of the portal vein may be purely coincidental or may result from a toxic condition of the blood in the splenic vein dependent upon the disturbed splenic function, or upon a general intoxication, or one affecting the portal area primarily. The changes in the hemolymph nodes and the new formation of lymphoid tissue are regarded as compensatory for the lost splenic function. It is also probable that a similar compensation is present in the bone-marrow, as shown by the changes described above. The anemia may be regarded as due either to an excessive destruction of red blood-cells by the endothelial phagocytes of the portions of the spleen still exercising the function of hemolysis in connection with an excessive activity of endothelial phagocytes in the hemolymph nodes and bone-marrow, or to a toxic hemolysis, or to a disturbance of balance between the destruction of hemoglobin and the elaboration of the products resulting from such destruction. From a careful study of the case we have arrived at the following:

Pathologic Diagnosis. Fibrosis of the spleen (*splenomegaly*), with beginning fibrosis of liver (*early stage of Banti's disease*); stenosis and calcification of portal vein, with extreme passive congestion of radicles of portal, particularly of splenic vein; chronic passive congestion of gastrointestinal tract, lungs, etc.; compensatory hyperplasia of hemolymph nodes and new-formation of lymphoid

tissue in retroperitoneal fat; increase of lymphoid marrow; acute fibrinous peritonitis following splenectomy; embolism of bone-marrow giant cells; general sclerosis and atrophy; secondary anemia; cholelithiasis.

CASE II.—Mrs. S., aged fifty three years, American, died 12.05 P.M., December 11, 1902. Autopsy by Dr. Warthin at 1.30 P.M., December 11, 1902.

Autopsy Protocol. Cadaver of slender build; no anomalies; no deformities. Right inguinal hernia. Abdomen on level of ribs. In the median line, between the umbilicus and pubes there is a laparotomy scar 14 cm. long, which is entirely healed with the exception of a sinus about 1 cm. long at about the middle of the scar. Pus exudes from the opening, which communicates by a fistulous tract with an abscess cavity in the abdominal wall.

Skin is pale, hair negative, teeth artificial. Over the back there is pale hypostasis. Transfusion punctures in pectoral regions. The muscles are greatly emaciated; on section they are deep brown and dry. There is no rigor mortis. The panniculus is of a fair amount. Edema is present over both ankles. Body heat is present.

Brain and spinal cord not examined.

The diaphragm is at the third intercostal space on both sides.

Mammæ atrophic. In the adipose tissue of the right there is a firm swelling about the size of a walnut, consisting of hyperemic and edematous fat tissue (transfusion area).

Apex of heart is behind the fourth rib, half-way between the left parasternal and nipple lines. The *mediastinal fat* is abundant and of an orange color; contains no enlarged glands. In the *thymus region* there is an abundance of orange-colored fat. No remains of thymus.

No fluid in *pleural cavities*. The left lung is adherent throughout, the adhesions being very dense over the base, where they have to be cut. Right lung is adherent by easily torn adhesions at apex and over the posterior surface and at the base; the adhesions here not so firm as on left side.

The *pericardial sac* is not tense; contains no fluid. Surfaces of pericardium are moist and shining.

The heart is much smaller than cadaver's right fist; weighs 272 grams, and measures 13 x 9.5 x 5 cm. There is a small, irregular, tendinous spot on the posterior wall of left ventricle; another near the apex, and one on the anterior wall of right ventricle. The subepicardial fat is increased. Heart muscle is pale brown, fairly firm. The right auricle contains currant-jelly and mixed clots and plum-colored fluid blood. The wall of the right ventricle measures 5 mm., 3 mm. of which are of fat. Right ventricle is empty. The left ventricle is empty, wall contracted; measures 20 mm. The left auricle contains plum-colored fluid blood and small red jelly-clots.

The *mitral valve* barely admits two fingers. Circumference of orifice, 8 cm. Flaps are thickened along proximal edges. Tricuspid barely admits three fingers; orifice measures 11 cm.; flaps negative. Pulmonary barely

admits thumb; orifice measures 6 5 cm.; flaps negative; aortic admits thumb easily; orifice 7 cm. in circumference; slight thickening of central segment.

The *aorta* shows beginning sclerosis, most marked about the coronary orifices. The descending branch of the left coronary artery is moderately sclerosed.

The *left lung* weighs 216 grams, and measures 17 x 13 x 3 cm. It is collapsed, pale, moderately anthracosed, and the pleura is covered with the remains of adhesions. On section the lung is pale, dry, almost bloodless, and yields almost no fluid on pressure. Beneath the pleura, particularly over the lower lobe, there are scattered a few dark areas of small size, which are firm on pressure.

The right lung is more voluminous and contains more air than the left. It weighs 256 grams, and measures 19 x 12 x 4 cm. On section it is more pink and moist over the middle and lower lobes; otherwise similar.

Bronchi negative. Bronchial glands moderately anthracosed. Pulmonary vessels contain large antemortem mixed clots and postmortem jelly-clots.

Thoracic aorta measures 5 cm. in circumference; contains small jelly and mixed clots. The azygos veins are greatly dilated.

Thoracic duct is distended with clear fluid.

Thoracic portion of esophagus contains a brownish fluid. The lower third shows marked varices; the esophageal veins and their anastomoses with the coronary veins of the stomach are markedly dilated. There are no evidences of hemorrhage from the esophageal mucosa. No erosions of the varices.

Mouth, pharynx, and *larynx* not examined. The cervical portion of the esophagus contains a brownish fluid. The thyroid is small and of firm consistence. On section it is pale and more brown than normal.

Cervical Hemolymph Nodes. In the deep cervical tissues numerous reddish, spleen-like glands resembling hemolymph glands are found. They are larger and appear much more numerous than normally.

Cervical vessels and nerves negative.

Abdomen. The *omentum* is adherent to the abdominal wall in the neighborhood of the umbilicus by easily torn adhesions, between which there is a fibrinopurulent exudate. The lower border is adherent to the anterior abdominal wall just above the pubes. The intestinal coils present scattered fresh fibrinous adhesions, particularly on the left side. From between the adhesions one and a half liters of turbid fluid containing many fibrin flakes are obtained, the greater part being taken from the left side below the spleen. The adhesions are strongest in the neighborhood of the incision. In the abdominal wall at this point there is a fistulous tract extending through the rectus muscle as far as the pubes, and communicating with the external opening in the laparotomy wound. Between the adhesions there is a collection of pus. The intestines in this region are firmly adherent to each other and to the abdominal wall. In one of the loops there is a darkened, thin, and softened area, but no perforation. The pelvis is filled with coils of small intestine which are adherent to the sigmoid and rectum. Between these adhesions there is about 50 c.c. of fluid similar to that in the abdominal

cavity, but more turbid and containing more fibrin. The transverse colon and cecum are moderately distended; the former is S-shaped, the lowest part two finger-breadths above the umbilicus. The *liver* is high and very small, the lower edge in the right parasternal line being three finger-breadths above edge of ribs and just at the tip of the ensiform in the median line. The left border is two finger-breadths to the left of the left sternal line. The *spleen* is greatly enlarged, filling in the entire left hypochondrium and projecting a hand's-breadth below the edge of the ribs. It is adherent to the diaphragm by several easily torn adhesions. The lower border of the stomach is three finger-breadths below the ensiform. There are easily-torn adhesions between the stomach, omentum, and hilum of spleen. No accessory spleen found in gastrosplenic omentum.

Spleen weighs 944 grams, and measures 19 x 14 x 7 cm. It is triangular in shape, broader at upper pole, the enlargement involving chiefly the upper third. The upper pole is slightly recurved. There is one deep notch at about the middle of the anterior border, extending nearly half-way across the organ. The capsule is thickened, particularly along the anterior margin, where there are flattened hyaline thickenings and the remains of stringy adhesions. The organ flattens somewhat, but is of increased consistence. On section it is firm and tough, creaks to the knife, pale, grayish-blue red, almost homogeneous, and shining, semitranslucent, but slightly granular in areas. Contains but little blood. The follicles are greatly diminished in number and in size—only a few can be seen. There is a diffuse fibroid hyperplasia of the reticulum of the pulp. The vessels at the hilum appear normal; veins collapsed.

Adrenals well preserved; no pathologic changes.

Left Kidney. Fatty capsule very rich in fat. Fibrous capsule strips easily; shape about normal; less plump than the right one; weighs 120 grams; measures 10 x 6 x 3 cm. Small, yellowish areas on the posterior surface. These are neither elevated nor depressed. On section they are found to extend through the cortex and medullary pyramids. In other respects resembles right kidney.

Right Kidney. Fatty capsule very rich in fat. Fibrous capsule strips easily. Surface of kidney smooth, mottled brownish-red and yellow; weighs 104 grams; measures 8½ x 5½ x 3 cm. Several yellowish spots, size of a pea, seen over the surface. On section cut surface is pale brownish-red, containing small yellowish areas size of a pepper-corn, and is more translucent than normal. Cortex measures 2 to 3 mm. Outlines of labyrinths and medullary rays well preserved. Vessels anemic; consistence firm; subpelvic fat increased; pelvis negative.

Ureters negative.

Bladder distended with cloudy urine. Mucosa negative.

Duodenum contains plum-colored, bloody fluid, with strong odor of H_2S. In this fluid are four large currant jelly-clots, weighing 12.2, 10.8, 7.3, and 6.1 grams respectively. Mucosa anemic, and presents no erosions or evidences of hemorrhage.

Bile Passages. Patent.

Small Intestine. The jejunum and ileum contain fluid similar to that found in duodenum, with yellowish clots. Toward the lower end of the ileum the fluid becomes thicker and darker in color. The mucosa is very anemic. No evidences of hemorrhage.

Appendix. Firm adhesions containing pus about the appendix. Lumen negative.

Large Intestine. Entirely filled with tar-like material. About the middle of transverse colon there is a small polyp. Mucosa is very anemic. No evidences of hemorrhage. The *rectum* is filled with a black, tarry, tenacious material adhering to the mucosa. In the latter are the scars of healed ulcers. No evidences of hemorrhage. Hemorrhoidal veins greatly enlarged, but collapsed. No evidences of hemorrhage from these.

Stomach. Contains 750 c c. of a thick, black fluid, composed chiefly of red blood cells and a few small red clots. The mucosa is thickened and covered with a thick, brownish mucus. About 14 cm. below the cardiac orifice there is in the posterior wall an erosion in the mucosa, having undermined edges, and about 3 mm. in diameter. Beneath this and under the neighboring mucosa there is a space about 2 cm. in diameter, filled with a fresh blood clot, and communicating with a ruptured vein in the posterior wall, a greatly dilated branch of the coronary veins. This is undoubtedly the source of the hemorrhage. All of the veins of the stomach wall are greatly dilated and tortuous, but are for the chief part collapsed and empty. The coronary veins in particular show a marked dilatation.

Liver. Small, about size of a child's head, nearly round, but irregular. Weighs 1856 grams.; its greatest dimensions are 23 x 17 x 11 cm. It is adherent to the diaphragm by very firm and tough adhesions. The surface is very irregular and nodular, particularly along the lower edge and near the ligaments. It contains numerous small hyaline areas and small translucent, glistening, brownish, points, varying in size from that of a pin-point to that of a pin-head. These are most numerous along the lower edge. Over the upper surface of the organ the capsule is 0 5 cm. thick, and firmly adherent to the diaphragm. The consistence is very firm; creaks on cutting. On section Glisson's capsule is greatly thickened in areas, the cut surface being mottled whitish and brown, the white areas corresponding to the dense hyaline connective tissue of the thickened Glisson's capsule. The increase of Glisson's capsule is, however, very irregular, being most marked in the central portion of the right lobe and beneath the external capsule. There appears to be a diffuse increase of connective tissue throughout the organ. The cut surface is slightly granular, the liver tissue showing as irregular islands surrounded by connective tissue. Surface is more translucent than normal. The outlines of the lobules cannot be made out. The branches of the hepatic vein are dilated, those of the portal nearly obliterated by the periportal increase of connective tissue. No icterus.

Gall-bladder is very small; size of a pigeon's egg. It is retracted above the

edge of liver. Tissues of the wall are thickened. It contains a very thick, glairy brownish-black bile; no stones.

Portal Vein. Just above the junction of the splenic and superior mesenteric veins the wall of the portal vein is thickened and contains calcareous plates. The lumen is stenosed, barely admitting tip of lead-pencil. The wall is irregularly thickened and shows lines of contraction radiating from the areas of calcification. The lumen is filled with a recent mixed thrombus, chiefly white, firm in consistency, and extending to the portal of the liver and into the smaller portal branches within the liver. No evidences of organization of the thrombus. All the radicles of the portal are enlarged and show thickened walls, the splenic vein in particular.

Pancreas. Smaller than normal. Lobules atrophic. Fatty infiltration between the lobules. Throughout the organ there are numerous whitish areas of fat necrosis in the interlobular fat. These are most marked along the upper border. In the great omentum about a hand's breadth below the greater curvature there is a red body the size of a cherry, embedded in the omental fat. It is rather soft and fluctuating, resembling a congested hemolymph node. On section it shows a small, firm, whitish nodule resembling epithelial tissue and suggesting pancreatic tissue, the remaining portion being made up of reddish lymphoid tissue and a small abscess cavity containing a brownish pus-like material. Small areas of fat necrosis are found in the fat tissue near by.

Mesentery. Mesenteric glands not enlarged. No hemolymph nodes found, except in root where there are a great number of reddish and bluish glands embedded in the mesenteric fat, probably hemolymph nodes.

Retroperitoneal Glands. Over 250 red, spleen-like glands found in the root of mesentery, retroperitoneal fat, about the renal vessels, behind and along the great abdominal vessels, and particularly along the brim of the pelvis. Along the left common iliac there is one 4 cm. long and as thick as a lead-pencil. A similar cord lies along the vena cava. The majority of the red glands are the size of a bean; others vary in size from that of a pin-head to that of a bean. On section they are firm, bluish-red and spleen-like; only a few show dilated sinuses and a softer consistence.

External Genitals. Negative.

Uterus and Appendages. Absent. (Removed at operation.)

Site of operation covered with fibrinopurulent exudate. About 50 c.c. of turbid fluid in pelvis.

Bone-marrow. Tibias opened longitudinally. Show no lymphoid changes. Red marrow in sternum and ribs hyperplastic.

Peripheral Lymph Glands. Prominent, but not enlarged.

Peripheral Bloodvessels. Femoral veins filled with recent thrombi: the left completely occluded by a clot of firmer consistency than that found in the right femoral. Lumbar and azygos veins greatly enlarged. (Material taken from all organs and tissues fixed in Flemming's, Müller's, Zenker's, mercuric chloride alcohol and formalin. Embedded in paraffin; stained with ordinary and specific stains.)

Microscopic Examination. Heart. Sections of heart muscle show brown atrophy. Fatty infiltration of right ventricle.

Lungs. Sections show atrophy and sclerosis of bloodvessels. Great numbers of bone-marrow giant cells in capillaries.

Spleen. Marked fibrosis of the reticulum of the pulp, with hyaline change of the newly formed connective tissue, the blood spaces being outlined by hyaline cords of varying thickness. The process is fairly uniform throughout the entire organ, although denser and more hyaline areas, with wholly or partially obliterated blood spaces, are seen in portions, particularly near the external capsule. The blood spaces are very prominent, and many greatly enlarged, some areas being cavernous. The lymphoid tissue of the pulp is very atrophic, and only small scattered collections of cells resembling follicles are seen. The majority of these contain hyaline masses. The blood spaces are lined by large hypertrophic endothelial cells, but these do not show any evidences of hyperplasia into the spaces. A few giant cells resembling those of the bone-marrow lie in the blood spaces (embolism?); a few normoblasts are also found. No unusual forms of cells observed in sections stained by special methods (triacid, polychrome, methylene blue, etc.). All the bloodvessels of the spleen are enlarged and show marked sclerotic changes and numerous nodules of calcification. A deposit of lime salts is also found in some of the hyaline masses of the follicles. Testing of many sections for iron with potassium ferrocyanide and hydrochloric acid entirely negative. No phagocytes containing blood pigment seen, and no free blood pigment.

Liver. Sections taken from different parts of the liver show that the greater part of the organ presents the picture of an atrophic cirrhosis. Glisson's capsule is greatly increased, and there is also a growth of connective tissue into the lobule. The periportal increase of connective tissue is, however, very irregular; in some areas it is very marked, in others it is but slight, small areas showing no cirrhotic changes. In other areas there is a central increase of connective tissue. The greater part of the lobules show central dilatation of the capillaries and atrophy of liver cells. Much of the connective tissue, particularly toward the surface of the organ, is hyaline and scar-like; in those areas showing less change the new tissue has more of a fibroblastic character and contains more small cells. There is a slight increase of the small bile-ducts. Liver cells are atrophic; those of the central portion of the lobule contain a very small amount of hematoidin. Iron test is entirely negative.

Pancreas. Sections show a fatty atrophy. Vessels are sclerosed. There is a small-celled infiltration of the interlobular fat, and localized areas of fat necrosis with small hemorrhages are present.

Body from Omentum. Sections show the red body found in the omentum to consist of three separate structures: A hemolymph node showing great numbers of phagocytes containing red cells in its blood sinuses; an accessory pancreas containing all the characteristics of pancreatic tissue, acini and areas of Langerhans. There is an increase of the stroma of the parenchymatous portion as well as of the islands, and an infiltration of fat cells. No

large duct leading from this accessory pancreas can be found, but a small duct can be traced leading into the third structure of the mass—an abscess cavity filled with a pus-like material, and having a wall of granulation tissue in which there are many large, thin-walled vessels. Small groups of necrosed fat cells are found in the neighboring tissue.

Stomach and Intestine. Sections show a chronic passive congestion with catarrhal inflammation.

Kidneys. Sections show atrophy, sclerosis of vessels, and localized areas of interstitial inflammation. Convoluted tubules show moderate cloudy swelling. Iron test wholly negative.

Hemolymph Nodes. These constitute one of the most interesting features of the case, judged from the pathologic standpoint. The changes may be summed up as follows: All the red glands examined show the structure of hemolymph nodes in varying stages of hyperplasia. They contain but few germ-centres. The blood sinuses are all very prominent and large, but the majority are only partly filled with blood. In some glands the sinuses are distended. They contain also great numbers of large hyaline cells having a yellowish or brownish color, and staining deep red with eosin. Some of the sinuses are completely filled with these cells. With the higher powers these cells are found to be phagocytes completely filled with red cells, or with the products of the disintegration of red cells. The nucleus of the phagocytic cell is usually pushed to one side, and shows more or less karyorrhexis. The outlines of the red cells can be distinctly seen in the phagocytes, and in many cases appear unchanged. In other phagocytes only hyaline droplets staining deeply with eosin or a brownish pigment are seen. The majority of the cells give a strong iron reaction with ferrocyanide and hydrochloric acid. In some there is a yellowish pigment which does not respond to the iron test (hematoidin?). Great numbers of mononuclear eosinophiles are found in some of the glands. Normoblasts and giant cells resembling those of the bone-marrow are found in large numbers in the blood sinuses. With the triacid stain numerous cells resembling myelocytes (neutrophile granulation and large excentric nuclei) are also found in the blood sinuses. In many of the retroperitoneal hemolymph nodes there are also large masses of hyalin which occupy the lymphoid areas between the blood sinuses. Many of these show calcification. Encapsulated caseous tubercle found in one gland. In the sections treated with ferrocyanide and hydrochloric acid the areas of calcification give a marked iron reaction, which is diffuse or very finely granular. A similar reaction is observed in many of the hyaline areas in which calcification has not taken place. The appearances suggest some connection between the hyaline masses and the blood destruction.

Lymphatic Glands. Atrophic; show marked hyaline change.

Bone-marrow. The normoblasts are increased and the giant cells greatly diminished in number. The reticulum of the red marrow appears hyperplastic and the blood spaces smaller. In the blood spaces and in the reticulum are great numbers of pigmented phagocytes, as in the hemolymph nodes.

Free pigment is also present. The iron test shows the pigment to be hemosiderin.

Tumor of Uterus (removed at operation). The tumor was found to be nearly completely calcified. After decalcification of portions sections were obtained showing it to be a myofibroma, with increase of the connective tissue, atrophy of the muscle, hyaline change, and calcification. Traces of atrophic muscle found throughout the dense hyaline tissue between the masses of calcification. Very few nuclei found in the hyaline connective tissue.

Summary of Pathology. The immediate cause of death is the anemia resulting from the hemorrhage from the eroded varix in the stomach wall. The dilatation of the stomach and splenic veins is the result of the portal obstruction. For the latter two etiologic factors are present, the stenosis and calcification of the portal vein and the periportal cirrhosis. It is impossible to decide the relative part played by these factors. The most important question is the relation of the splenic condition to that of the liver. It is, however, impossible to decide, positively, which is the primary condition, the splenic fibrosis or the cirrhosis of the liver. Because of the more advanced stage of the splenic fibrosis, the dense hyaline character of the new tissue formed in the walls of the pulp spaces, the areas of hyalin and calcification, the greater atrophy of splenic parenchyma, etc., it seems very probable that the splenic process is older than that of the liver. If this is the case the question also arises here as to the relationship between the changes in the spleen and those in the portal vein. Is the splenic fibrosis primary, or is it secondary to the disturbance of the splenic circulation following thrombosis and the resulting stenosis of the portal? This question, unfortunately, cannot be positively answered. The portal condition is, undoubtedly, the result of an old pylephlebitis and thrombosis, but it is impossible to determine if it preceded the splenic condition or is secondary to some toxic condition of the portal blood, dependent, possibly, upon a primary change in the spleen or upon a general toxemia.

The changes in the hemolymph nodes are to be interpreted as compensatory for the lost splenic function. The complete absence of blood pigment or of phagocytes in the spleen may explain the great excess of hemolysis occurring in the hemolymph nodes and bone-marrow. The evidences of phagocytic hemolysis in the hemolymph nodes presented by this case show a much greater blood-destruction

than that occurring in these glands in any of the cases of pernicious anemia observed by the writer. In spite of so great a hemolysis no hemosiderin is found outside of these glands and the bone-marrow. Iron tests of liver, spleen, and kidneys show not a trace of iron. The hemolysis is therefore different from that occurring in pernicious anemia, and is most probably not a pure hemolysis, but is to be interpreted as a *compensatory* one. The anemia may then be explained as due to an excess of hemocytolytic hemolysis over that of splenic, or to a disturbance in the elaboration of the products of blood-destruction.

From the study of the case we have arrived at the following:

Pathologic Diagnosis. Splenic fibrosis with cirrhosis of the liver (late stage of Banti's disease), gastric hemorrhage, anemia, stenosis and calcification of portal vein, chronic passive congestion of portal system, ascites, peritonitis, hyperplasia of hemolymph nodes, with excessive hemolysis, hyperplasia of red marrow, giant-cell embolism, general atrophy and edema, tuberculosis of retroperitoneal gland, accessory pancreas, fat necrosis.

Comparison of Cases. Both cases present the following common features:

1. Splenic fibrosis.
2. Hepatic fibrosis.
3. Stenosis and calcification of portal vein.
4. Chronic passive congestion of portal system.
5. Sclerosis of vessels, particularly of portal area.
6. A marked tendency to hyaline change and calcification throughout portal area.
7. Hyperplasia of hemolymph nodes and bone-marrow and new formation of lymphoid tissue in retroperitoneal fat.
8. Secondary anemia.

Comparing the two cases the splenic fibrosis in Case I. represents an earlier stage: that in Case II. a much more advanced stage. In Case I. the liver changes are relatively slight, a beginning fibrosis. In Case II. they are marked—an advanced cirrhosis, a cirrhosis, however, which does not present all the features of an ordinary atrophic cirrhosis. The changes in the portal vein in both cases were at the same site and of about the same degree. In Case I. the more irregular character of the vessel wall, the bridging strands of tissue across

the lumen of the vein, might indicate a more recent process. The chronic passive congestion of the portal is more marked in Case II. than in Case I., as shown by the greater development of anastomoses and the pronounced varices in esophagus and stomach leading to the fatal hemorrhage in the former case.

In Case I. the hyperplasia of the hemolymph nodes is not nearly so marked, and in these glands there are not the evidences of the pronounced hemolysis seen in Case II. In Case I. the spleen contains some phagocytes and blood pigment. In Case II. none of these were found in the spleen. These differences may also be interpreted as indicating an early stage of the process in Case I. and a later stage in Case II. The pathologic findings, therefore, would appear to warrant the diagnosis of early and late stages of Banti's disease.

In both cases (unlike some others described under the head of splenic anemia or Banti's disease) there is no clinical evidence and no positive proof of the existence of syphilis. On the contrary, the history of both cases excludes the possibility of this disease.

The important question as to the relationship between the splenic condition and the stenosis of the portal remains to be settled. Is the splenic fibrosis a distinct pathological entity or is it a secondary process? The changes in the spleens of the two cases do not represent any features that could not be explained by a chronic passive congestion of marked degree; that is, it is possible for such a hyperplasia of connective tissue to follow a severe and long-continued passive congestion, as is sometimes the case in the lung, liver, etc. This question, however, cannot be answered by these two cases. It can only be said that there is a possibility that the clinical picture of splenic anemia or Banti's disease may be caused by a stenosis of the portal vein due to old phlebitis and thrombosis and the resulting stenosis.

On turning to the cases of splenic anemia reported in the literature under such heading we find that the condition of the portal vein is not mentioned at all, or so briefly as to convey the impression that the vessel had not been carefully examined. In the older literature there are, however, a number of very suggestive cases similar to the two described above, and reported under the head of "Thrombosis," or "Stenosis of Portal Vein, with Hypertrophy of the Spleen." The descriptions given of these cases, though incomplete and meager, when judged from modern standpoints of diagnosis, suggest very

closely the cases now described as splenic anemia. Among these is one reported by Sir Andrew Clark (*Trans. London Path. Soc.*, 1867). The patient had suffered previously from "biliousness" and intestinal hemorrhages: died of gastric hemorrhage. Skin sallow, body very fat. Autopsy showed spleen to be three times normal size; liver "thinner" than normal; wall of portal vein contained calcareous plates; in the lumen there was a fresh thrombus.

It is possible that this and some of the similar cases reported in the literature, as well as some of the cases of cirrhosis with changes in the portal vein, may represent the same morbid processes as do our two cases, and that they should be placed in the category of splenic anemia.

Conclusion. The two cases reported above present, clinically and anatomically, the pictures of an early and a late stage of Banti's disease—an older fibrosis of the spleen with a more recent fibrosis of the liver. Both cases present also the condition of stenosis and calcification of the portal vein. Is the latter the primary condition, to which the splenic fibrosis follows secondarily, or is it the result of a portal or general intoxication, to which the splenic and hepatic fibrosis are also due? The solution of this problem must wait upon the observation and investigation of other similar cases.

DISCUSSION.[1]

Dr. Cabot: There are two points on which I wish to speak. First, regarding the types of leukemic blood. Out of seventy-six cases that I have seen there has never been any reason to believe that the two types were fused or mixed. All were clearly myelogenous or clearly lymphatic. The literature has not convinced me to the contrary, as in the cases where a mixed leukemia has been reported the reported blood examination has not been satisfactory. I am not satisfied with Dr. Kinnicutt's case in this respect to-day. I cannot understand about great differences between the count of myelocytes in the blood and that in the marrow. It seems to me that this must be a mistake. At any rate, I should want further evidence in regard to it. While it is possible that there may be mixed cases, it seems to me that the fact is not established.

[1] Dr. Kinnicutt's paper has not been received for publication in this volume, but it is impossible to eliminate the references thereto and maintain the integrity of the discussion. —Recorder.

Secondly, I wish to raise the question whether lymphatic leukemia is to be considered as an entity? The myelogenous type certainly deserves to be so considered, but I cannot make up my mind that the lymphatic does. A similar condition following whooping-cough is almost indistinguishable at times from lymphatic leukemia, but the patients recover in a few days. In a case of a young physician who wounded himself at an autopsy, a general infection of the lymphatic glands followed, with a marked increase of lymphocytes, absolute and relative, which alarmed us very much. The whole thing cleared up in about a week. Are we to call these cases lymphatic leukemia; if not, why not; and if so, is it not a very loose clinical entity?

Dr. Peabody: I should like to refer to a case without enlargement of the lymphatic glands. This was a woman, about fifty years of age, with a history of no definite symptoms, but merely of not being very well for some years. She developed a bronchopneumonia, and entered the hospital with the right lung considerably involved. We had no suspicion of any other condition until it was developed by a routine blood count. The spleen was just palpable. There was one axillary gland about as large as a grain of wheat, but no other enlargement of the glands. We examined her blood, as a routine matter, and found that she had 150,000 white cells. A differential count showed 91 per cent. mononuclear. On the sixth day of her pneumonia the white cells numbered 210,000, and in two weeks after defervescence they had fallen to 168,000. It is of interest as showing the effect of pneumonia in increasing the number of white cells in leukemia, as it does in health. She went through her pneumonia without much difficulty.

Dr. Herrick: It has been my fortune to have seen nine cases of lymphatic leukemia, and six of these were of the acute variety. These six acute cases were in most respects typical. Yet in two the small mononuclear form of lymphocyte prevailed. In two cases there were, contrary to the rule, large numbers of nucleated red blood cells, chiefly the normoblasts. Clinically all six resembled the acute infections, with fever, hemorrhagic tendency, palpable spleen. Four had marked angina, with exudate upon the tonsil. The anemia was, without exception, rapid and progressive.

The resemblance of these cases to two cases of septicemia, with rapidly progressive and fatal anemia, was striking. In these cases of sepsis, however, there were not the ordinary blood findings of lymphatic leukemia—merely a slight relative increase in the lymphocytes. The two cases of septicemia started—one in a tonsillar abscess and the other in an induced abortion—death following in two weeks in each instance, and the blood count running as low as 1,000,000. Were it not for the fact that the glands were not enlarged, and that there was but a slight relative increase in the mononuclear leukocytes, one would have diagnosed lymphatic leukemia. These cases of acute sepsis, with grave anemia and lymphocytosis, resembled the case in a child reported not long ago from Leube's clinic.

Dr. Fussell: I reported a case some three years ago that began with the ordinary symptoms of typhoid—headache, continued fever, and diarrhea. There was only a moderate enlargement of the spleen; no macroscopic enlargement of the lymphatic glands. It was only after routine examination of the blood that anything but typhoid was thought of. At the post-mortem the spleen was found to be only moderately enlarged. The Peyer's patches were enlarged, inflamed, and ulcerated, exactly as in typhoid fever. Anyone not having made an examination of the blood would have called it typhoid fever.

Dr. Welch: These cases have a peculiar interest in reference to the theory of the origin of the lymphocytes. The study constitutes now the principal attack upon Ehrlich's theory as to the origin of the lymphocytes. I have been much interested in the study of the subject, and in one case, carefully reported, the lymphatic glands were not enlarged and the lesions were practically, as in Dr. Kelly's case, in the marrow, and it seems to point to the fact that the lymphocytes can make cells in the marrow. The parent cell of the polynuclear leukocyte and the lymphocyte is probably the same. It is capable, in embryonic life, of producing other kinds, but ordinarily in adult life of producing only neutrophiles.

Another point is the question of ameboid movement of the lymphocytes. I have always held that the evidence in support of their movement was conclusive. I was led to that belief by the observations of Gilchrist in urticaria. They accumulate within fifteen minutes of the application of the irritant. There must be active migration of the lymphocytes.

As to the terminal infections in leukemia, it is most frequent where we make bacteriologic examinations. I am sure we shall find in the great majority of instances terminal infection. In several instances there have been infections of the streptococcus, and in one case section of the lymphatic glands showed this.

I was interested in the case last reported by Dr. Dock, the case of sclerosis and calcareous degeneration of the portal vein. I recall a similar case: a man who died in New York of gastric hemorrhage, and in that case there was marked sclerosis of the walls of the vessel and calcareous degeneration. The changes in the spleen were well marked, and there was a moderate degree of sclerosis of the liver. I think it would be very interesting if these cases were carefully gone over. They represent a distinct group—cases that look as if they were primary forms of sclerosis of the portal vein in association with calcareous degeneration, and a careful study of them would be extremely interesting.

Dr. Osler: We must recognize two distinct groups with different clinical pictures. One group runs a course in ten or twelve weeks; the other may last for as many years. The acute diseases resemble acute septicemia, and I have at present a patient in my wards with the picture of an acute infection

—hemorrhages, fever, severe angina, and lymphocytosis, with large mononuclears of about 90 per cent. The cases presented by Dr. Dock and Dr. Warthin illustrate the difficulty of differentiating certain cases of splenic anemia and cirrhosis of the liver. Calcification of the portal vessels may occur in advanced cirrhosis or in chronic enlargement of the spleen.

Dr. Kelly: I have only to emphasize what I have already said in my paper —the great necessity of a renewed and thorough study of the lymph glands and lymphoid tissues in general. Among the several points especially requiring elucidation are the relations of lymphocytosis (of which we know comparatively little) to lymphocytic leukemia and the histogenesis of the blood corpuscles in general. We shall have to determine also whether the circulating lymphocyte in leukemia is the same as the circulating lymphocyte in health. I believe, furthermore, that all cases of atypical and mixed (or intermediate) leukemia should be carefully studied and reported. It is a pleasure to know that some of the opinions that I have expressed are entertained by such a man as Dr. Welch. Finally, the clinical resemblance of some cases of leukemia to typhoid fever will bear further investigation.

Dr. Kinnicutt: In regard to the suggestion of the possibility of error in the blood examinations, I would say that they were all made by the pathologist of the hospital. I should be more inclined to think that there might be error in the examinations of the marrow than in the examinations of the blood.

Dr. Dock: Among leukemic cases it is true that we can distinguish two great types, but it seems to me we must admit there are still other varieties. I have had one case in which the general picture was that of mixed-cell leukemia, but in which the cells varied widely from those usually found. Grawitz has mentioned a case closely similar to mine, and within the last few years a number of atypical cases have been described. As to the lymphatic form, I called attention at the Moscow Congress to the peculiarities of the chronic cases. There was nothing really new in that since Neumann had described the disease long ago, and Askanazy and others later, with reference to the more recent methods of studying blood, but I think the differences in the cells found in the acute and chronic cases are still not sufficiently borne in mind. Although it is natural to call the new leukocytes in the chronic cases lymphocytes, they show certain points of difference as compared with normal lymphocytes. While variations of size and form are seen, the cells do not show so much variation as do the cells in the acute cases, making it, as Dr. Kinnicutt has stated in his chart, futile to classify them. With reference to the point made about the so-called myelocytes in Dr. Kinnicutt's case, I think, too, that another examination of the preparations should be made, but I am not unwilling to believe the cells may prove to be genuine myelocytes of Ehrlich. On the other hand, there may have been such a condition as A. Fränkel had to do with in his interesting and

extensive series of cases, and the so-called myelocytes may have been myelocytes in fact, but not those so named by Ehrlich. I have examined Fränkel's preparations, through the kindness of Prof. Fränkel, and also many other preparations from cases under the care of many observers. I have found that the cells in question are what most people call lymphocytes, which they are in the morphologic sense; but, on the other hand, they may be marrow cells, such as Cornil found in bone-marrow long ago, and as Dr. Welch has suggested as possible. I am strongly of the opinion that in leukemia the new cells can come from any of the new-formed tissue, whether in bone-marrow or elsewhere, though obviously in most cases the bone-marrow is earliest affected. Whether the cells get out by ameboid movement or in some other way is simply a matter of detail.

Apropos of the resemblance of certain cases of acute leukemia to typhoid fever, we had an interesting case in which not typhoid, but a disease sometimes hard to distinguish from it—namely, appendicitis—was suspected and an operation made. The symptoms were most characteristic, but there was a leucocytosis of 95,000. No differential count being made, the striking points of contrast from an ordinary leucocytosis were not used in the diagnosis. Though many surgeons look upon minute blood examinations as a waste of time, or worse, such a case illustrates their great practical value, and with so convenient a stain as Wright's there seems no excuse for neglecting them.

Dr. Warthin: I only want to say that in our first case it could not have been secondary to the condition of the liver, as the changes in the liver were slight indeed.

AN EXPERIMENTAL STUDY OF NEPHROTOXINS.

By RICHARD M. PEARCE, M.D.,
OF PHILADELPHIA.

(From the Pathologic Laboratory of the University of Pennsylvania.)

CONTENTS.

Introduction. Methods. On the production of autonephrotoxins by unilateral ligation of (*a*) ureter, (*b*) renal vessels, and (*c*) by unilateral nephrectomy. On the production of isonephrotoxins by unilateral ligation of (*a*) ureter, (*b*) renal vessels, and (*c*) by unilateral nephrectomy and injection of (*d*) emulsion of kidney, (*e*) normal serum (control). On the production of heteronephrotoxins by injection of (*a*) rabbit's kidney into guinea-pig, (*b*) guinea-pig's kidney into rabbit, (*c*) dog's kidney (washed and unwashed) into rabbit, by infusing (*d*) serum of dog having received nephrotoxic serum, (*e*) inactivated rabbit's nephrotoxic serum, (*f*) serum prepared respectively from kidney cortex and medulla, (*g*) hemolytic serum, (*h*) hepatotoxic serum, (*i*) normal rabbit's serum (control). On spontaneous nephritis in dogs. On the toxicity of the serum of dogs, with spontaneous nephritis. On the production of chronic renal disturbances by multiple injections of (*a*) heteronephrotoxic serum, and (*b*) serum of dogs with spontaneous nephritis. A study of the blood pressure in nephrotoxemia. On the toxicity of renal parenchyma. The specificity of cytolysins. Summary. Bibliography.

The energy with which the study of the cytolysins has been pursued has added in a relatively brief period many important facts to our knowledge of the cellular reactions. The number of cytolysins now known and more or less fully studied covers all, with few exceptions, of the tissues and organs of the animal body.

A small part only of these cytotoxins have been exhaustively investigated, and of none can it be said that the last word has been spoken. In a few instances, as in the case of the hemolysins and spermotoxin, the studies have been so minutely pursued as to supply a definite basis of knowledge; while the greater number of somatogenic cytotoxins, such as hepatotoxin, adrenaltoxin, nephrotoxin,

thyreotoxin, pancreastoxin, have either a doubtful existence or have yet to be proven to possess specific properties.

In many instances the difficulties of demonstrating activity and specificity are considerable and not readily overcome. The actions of an hemolytic serum is quickly shown by the laking *in vitro* of the blood, of a spermatoxin or trichotoxin by the cessation of motion, a clumping and, perhaps, solution of the cells. But for most of the organic cells these tests are inadequate or do not apply, and the reactions of the living cells within the body can alone be taken as a sign of cytotoxic activity. These reactions consist of degenerative lesions demonstrable upon microscopic examinations, or symptoms of disease referable to the action of the poison. Unfortunately these last criteria offer opportunities for differences of opinion and observation which are not readily controlled.

In some organs, however, an altered physiology affords a trustworthy indication of injury, as in the albuminuria and excretion of casts after injection of a nephrotoxin and the hemoglobinuria following that of a hemolysin. The study of cytotoxins which produce such functional disturbances offers, therefore, a promising field for research and the possibility of elucidating certain obscure pathologic phenomena. Of such cytotoxins, nephrotoxin is perhaps the most satisfactory, and promises the most trustworthy results. A review of the literature shows that this one has been studied more extensively than other somatogenic cytotoxins; and if we accept all that has been written its effects explain not only the etiology and pathology of nephritis, but also the associated circulatory changes, heart hypertrophy, and uremia. A critical study of many of the reports leads, however, to the impression that the writers have made extravagant claims, based upon insufficient experiments without satisfactory control. Little of the work has been accompanied by careful bacteriologic tests; and while in some the examination of the urine has been considered most important, in others the histologic study of the kidneys has been neglected; and in all little attention has been paid to the action upon the kidney of other kinds of serums than those produced by immunization with the kidney cells.

In spite of many serious omissions and a one-sided point of view, general uniformity of results is still to be made out. This fact has led me to repeat the work in all its phases, using, at the same time, a

sufficient series of controls. I have attempted to produce autonephrotoxins by injuring one kidney through various operative procedures, with the expectation of finding lesions in the opposite kidney. The serum of such animals theoretically should be isonephrotoxic for other animals of the same species, and has been investigated as such. The production of isonephrotoxins through immunization has also been attempted. The formation of heteronephrotoxins by means of immunization to various alien renal cells has been carefully studied; and in determining the effect of these several substances systematic examinations of the urine and of the histology of the kidney have been made. The effect of the nephrotoxins upon the blood pressure has been investigated by means of the kymograph, and an effort has been made to determine accurately the degree of toxicity of renal parenchyma. An unexpected interest has been added to the investigation by the observation that dogs frequently suffer from a nephritis of undetermined origin. This condition, which, as far as I am aware, has not attracted the attention of recent writers on the subject of nephrotoxins, has been carefully considered, and the results of the injection of the serum of such animals into healthy dogs has been studied in some detail. The gradual extension of the investigation along unexpected lines, and the numerous controls necessary to an adequate understanding of the results obtained, have transformed a problem which at first seemed a simple one into a comprehensive study of experimental degenerations and inflammations of the kidney due to cell products. The facts given here are based on more than 200 experimental protocols. The order in which the various phases of the work will be considered is indicated in the preceding summary:

METHODS.

Immunization. In immunizing animals against body cells the greatest danger is that of infection. The various manipulations necessary for the removal of organs, their disintegration, and final injection offer many chances of contamination. The chief requisite is therefore ceaseless attention to the details of asepsis during the carrying out of these processes. In my early work the mortality among injected animals was comparatively high, but after the development of a more perfect method of work this was reduced to a

negligible figure. The question of the preparation of the organs for injection is an important one. Various grinding and compressing devices have been described. I at first used a sausage machine, but this I soon discarded for a mortar, pestle, and fine wire tea-strainer. This method, owing to its simplicity, is worthy of description. The tea-strainer is laid in the mortar and receives the finely-divided kidney fragments, and, after the addition of salt solution, the disintegration is completed by gentle grinding with the pestle against the rough surface of the strainer. When the strainer is removed the organic emulsion remains in the mortar. It is rare that fragments large enough to plug the needle of the syringe pass through the wire mesh. Manipulation, with the attendant danger of contamination, is thus reduced to a minimum, and the apparatus mentioned can be more readily sterilized than the sausage machine.

The injections of kidney substance have been intraperitoneal. The absorption under these circumstances is more rapid and thorough than in subcutaneous injection, and, although the mortality is, perhaps, greater, one does not have to deal with the possible complication of long-continued, subcutaneous suppuration.

Three, four, or five injections have usually been given at intervals of from seven to ten days, the amount of kidney substance being, as a rule, increased at each injection.

Bleeding. The first bleeding has been made seven to ten days after the third injection; other bleedings following after an interval of a few days, or after the fourth or fifth injection. Repeated bleedings have been rendered easily possible through the use of the Lataple tube and the holding device invented by Dr. J. E. Sweet. Using this method, the blood is easily obtained in a sterile condition, and yields 40 to 50 per cent. of serum. Rats were bled from the abdominal aorta by means of a pipette. The serum thus obtained has been injected, in the case of the rabbit, into the ear-vein; in the guinea-pig and rat, the peritoneal cavity; and in the dog, the internal saphenous or femoral vein.

Urine. All animals have been isolated from one to seven days before inoculation for the purpose of a control examination of the urine. I regard this as most important, especially in dogs, on account of the frequency with which they show a spontaneous albuminuria or nephritis. After the injections daily tests for albumin and daily

microscopic examination of the sediment have been the rule. The color, amount, and reaction of the urine have been noted in cases where such observations were considered important. For demonstrating albumin the nitric acid and heat tests were employed.

Histology. As a matter of routine, tissues have been preserved in Zenker's and in Fleming's fluids. Those preserved in the former have been stained with hematoxylin and eosin after celloidin embedding; in the latter by safranin after paraffin embedding. Safranin has a strong affinity for cell granules, and has therefore been of great service in studying the changes in these bodies. Still other staining methods have been used as occasion required.

Bacteriology. Routine bacteriologic examinations have, as a rule, supplemented the postmortem examination of all animals, and they have been of great value in excluding infection as a possible cause of the lesions produced by the toxic injections.

ON THE PRODUCTION OF AUTONEPHROTOXINS.

Several French and Italian investigators claim that as the result of the degeneration of kidney cells following the ligation of the renal vessels or the ureter a deleterious action is exerted on the opposite kidney. This they attribute to the accumulation of toxic substances in the blood, which substances they call autonephrolysins or autonephrotoxins.

The first author to produce such a substance by ligation of the ureter was Néfédieff, but as he used the serum to inject into other animals of the same species, the action is to be regarded as isotoxic. He did not examine histologically the kidneys of animals upon which he operated.

A fuller study of this subject was made by Castaigne and Rathery. They ligated a ureter or the vessels or entire pedicle of one kidney in the rabbit and found constantly, as they state, certain degenerative changes which they denominate protoplasmic cytolysis. This change consists in a partial or complete disappearance of the granules normally present in the cells of the convoluted tubules, the nuclei of the cells remaining normal or becoming pyknotic or fragmented. It is noted that during the life of the animal albuminuria is present, and similar histologic and other alterations are produced by a unilateral

nephrectomy, which is followed by the injection of the removed kidney, finely divided, into the peritoneal cavity of the animal. They failed to find changes of the sort described after simple unilateral nephrectomy.

Ascoli and Figari set up, by means of unilateral ligation of the ureter and unilateral nephrectomy, intermittent albuminuria. They do not give the results of the histologic examination of the kidneys.

Bertenson carried out various operations on the kidney with the effect of producing hypertrophy, degeneration, or inflammation of the opposite organ.

The most recent work on this form of toxic nephritis is that of Albarran and Bernard, whose results have been mainly negative. Of four animals in which they ligated the ureter, one only presented degenerative changes in the opposite kidney. Of a series of experiments carried out by them upon rabbits and dogs, some of which lived eight months, for the purpose of studying hydronephrosis, in no case were degenerative changes found in the opposite kidney.

I have repeated on the rabbit and the rat the experiments described under conditions of proper control.

Ligation of One Ureter. *Rabbit.* The ureter was ligated in five animals about 2 cm. from its origin. One died within forty-eight hours of a peritoneal infection. The other four were killed ten, twenty-two, forty-nine, and eighty-eight days, respectively, after the operation. In all albumin could occasionally be detected in the urine in very slight traces, but usually for a few days only after operation. In no instance was it found after ten days had elapsed. The sediment never contained casts or other evidences of renal disturbance.[1]

In all the animals a loss of weight varying from 50 to 300 grams occurred. With the exception of one animal in which a pyelonephritis developed, all the ligated kidneys showed hydronephrosis varying in degree according to the length of time which had elapsed

[1] I have not infrequently found in the rabbit's urine long, thin, wavy shreds, suggesting unusually long granular casts. These bodies, however, disappear upon the addition of acetic acid, and, as the superimposed granular material is largely composed of very fine crystals, I have come to the conclusion that they are shreds of mucus to which are adherent the crystalline salts of the alkaline urine. It is possible that this mucus may be associated with disturbances in the lower urinary passages. I do not believe it indicates renal changes, and have entirely disregarded the presence of the structures in the descriptions.

since operation. In the animals killed after forty-nine and eighty-eight days, respectively, a distinct hyperplasia of the opposite kidney was present.

Histologic Examination. The kidneys which were left behind showed the following: In the rabbit with pyelonephritis, killed on the twenty-second day, cloudy swelling and fatty metamorphosis; in the others no appreciable change. The kidney sections of the rabbits killed on the forty-ninth and eighty-eighth day could not be distinguished from those of normal rabbits. The observation of Castaigne and Rathery of a diminution in cell granules in the convoluted tubules was not confirmed, but, on the contrary, the granules in the specimen of the kidney from the eighty-eighth day rabbit appeared to be increased, while in the rabbits killed on the tenth day an increase was certainly present. A protocol illustrating this series of experiments follows:

Rabbit 57.[1] March 14th, isolated; weight, 1950 grams. March 15th, 16th, and 17th, urine free from albumin; sediment negative. March 18th, weight, 1940 grams. Left ureter ligated 1.5 cm. from its origin. Rapid recovery from operation. March 19th. Urine, high colored; distinct trace of albumin; sediment contains few red blood corpuscles. March 20th. Urine, high colored; faint trace of albumin; sediment contains very few red blood corpuscles. March 21st. Light-colored urine; no albumin; sediment, negative. Daily examination of the urine until April 29th gave negative results. Rabbit bled on April 7th and 29th, and killed on this last date. Weight at death, 1865 grams.

Autopsy. Operation wound perfectly healed; left ureter above ligation dilated to a diameter of 0.6 cm., and contains a clear, yellow fluid with a few pale flocculi; below ligature it forms a thin, fibrous cord. Left kidney transformed into an oblong cyst 13 x 10.1 cm. The kidney substance has entirely disappeared except at the outer aspect, where it persists as a thin, grayish-yellow layer. Right kidney slightly enlarged, measuring 3.1 cm. in length; on section, normal. Coccidiosis of liver. Other organs normal. Histologic examination of the right kidney negative.

Ligation of Ureter. *Rat.* In this series the technic was followed as in the case of the rabbit. An amount of urine sufficient for analysis was obtained by placing the rats in wire-gauze cages with slanting tin bottoms. Traces of albumin were found during the first few days after operation. Casts were never found, and the albumin

[1] The operation was performed under ether anesthesia.

usually disappeared after the first week. One rat was killed on the thirty-third day and two on the forty-fourth day. Aside from the slight hyperplasia, the opposite kidney was unchanged. The following protocol is an example.

Rat 1. October 29th, isolated. October 30th urine contains no albumin, and the sediment is negative. October 31st, under light ether anesthesia, left ureter ligated 1 cm. from its origin. November 1st, good recovery from operation; November 2d, slight trace of albumin;[1] November 3d and 4th, no albumin. November 5th, trace of albumin; November 6th and 7th, no albumin; November 8th, 9th, 10th and 11th, faint trace of albumin. From this time until December 3d the urine remained free of albumin, except on November 23d, when a faint trace was detected. On December 3d the animal was bled and killed.

Autopsy. Perfect healing of abdominal wound; peritoneum clean. Left ureter above ligature greatly dilated and continuous with thin-walled sac corresponding to capsule of kidney. This capsule is thickened, grayish-white in color, and presents thin islands of kidney substance only along its outer border. This hydronephrotic cyst measures in length 2.7 cm., and in width 1.4 cm., and contains a clear straw-colored fluid. Right kidney is congested and swollen. Other organs normal. Histologic examination of right kidney reveals an increase of granules in the cells of the cortical tubules.

Ligation of Renal Vessels. *Rabbit.* The entire pedicle of the left kidney was ligated in four animals. They were killed ten, forty-four, forty-eight, and eighty-seven days after the operation.

The same slight loss of weight was observed in these animals as in those in which the ureter was ligated, and the same occasional albuminuria. The examination of the sediment was uniformly negative except in one animal, in which for ten days after the operation albuminuria was accompanied for a few days by morphologic elements in the sediment pointing to a progressive liquefaction of the tied-off kidney. At the postmortem examination it was found that the ureter had not been included in the ligature. The protocol of this experiment follows:

Rabbit 59. March 11th isolated. March 12th, 13th, 14th, and 15th, urine normal. March 18th, weight 1920 grams. Vessels of left kidney ligated, ureter remaining free. March 19th, urine dark red in color; well-marked

[1] In order to avoid repetition, the examination of the sediment is not noted when negative. It is to be understood that the sediment was always examined when albumin was found.

ring of albumin; sediment contains innumerable complete kidney tubules, many renal cells, single and in clumps; no red blood corpuscles.[1] March 20th, dark red, opaque urine; when filtered, deep dark color, dense ring of albumin. Sediment: much renal epithelium, free and in clumps; tubular arrangement frequent; no red corpuscles or casts. March 21st, 22d, and 23d, urine dark red in color; marked ring of albumin. Sediment: few small clumps of renal cells, much granular detritus, no red blood corpuscles or casts. March 25th, 26th, 28th, and 29th, urine of normal color; gradually diminishing amount of albumin, usually only a trace. Sediment negative, except for an occasional renal cell. March 30th to April 9th, urine normal. April 9th, bled from left jugular vein. April 10th and 11th, reappearance of faint trace of albumin with few leucocytes and disintegrated cells in sediment. From this time until May 5th the urine remained normal except from April 18th to May 3d, when a trace of albumin, some leucocytes and granular cells were observed. May 5th, weight 1610 grams. Bled and killed.

Postmortem Examination. Left kidney transformed into a thick-walled sac, two-thirds the size of normal kidney, containing soft, pultaceous material. The wall of ureter is thickened, its lumen dilated, and it contains a thin, grayish fluid which, microscopically, is composed of leucocytes and granular cells and débris. Right kidney swollen, congested; length, 3.1 cm.; normal on section. Other organs normal. Culture from left kidney sterile. Histologic examination of right kidney showed normal structure only.

The following protocol illustrates the comparatively negative character of the urine in those experiments in which the ureter as well as the vessels were ligated:

Rabbit 11. November 22d, isolated. Weight, 2387 grams. November 23d and 24th, urine normal. On November 24th the entire pedicle of left kidney

[1] The color of this urine was obviously due to the presence of blood pigment. No red blood corpuscles, however, or at most only a few "shadows," could be found. It seemed probable that the condition was a true hematuria, but that the hemoglobin of the red corpuscles had been set free by the alkaline urine. This was suggested by Jordan's observation that the hemolyzing action of so-called "pyocyanolysin" is due to the alkalinity of the culture fluid. As the rabbit's urine is normally alkaline, it seemed probable that a similar action might be expected. A series of tests made with rabbit's urine and red blood corpuscles proved the correctness of this supposition. The rapid solution of the hemoglobin and its reduction to methemoglobin give the urine an appearance similar to that observed in the above experiment. In hematuria in the rabbit, therefore, the appearance of the urine depends on the length of time which has elapsed since the urine was voided; if examined immediately, the red corpuscles may be found in the sediment; if after several hours have elapsed, it has the dark red, port-wine color characteristic of hemoglobinuria.

was ligated. November 26th and 27th, faint trace of albumin; sediment negative. November 29th to December 6th, no albumin. December 7th and 8th, slight trace of albumin. From this time until February 19th, when the rabbit was killed, the urine remained free of albumin except for the two days (January 29th and 30th) following the first bleeding. Weight when killed, 2390 grams.

Autopsy. Left kidney is but one-half the size (length, 1.8 cm.) of the right, and lies in a thick capsule of fat tissue which entirely obscures the ligature. The capsule of the kidney is greatly thickened. On section, a thick, fatty, atheromatous material corresponds to the position of the cortex. The medulla is recognized as a triangular, soft-grayish-red, slightly striated mass, freely movable in the centre of a completely necrotic material. Cover-slip preparations and cultures demonstrate the absence of micro-organisms. Right kidney is larger than normal (length, 3.5 cm.). On section, the cortex apparently is increased.

Histologic examination of the left kidney showed complete necrosis of the cortex with entire disappearance of tubules. In the medulla, fatty and necrotic tubules could be distinguished. In the right kidney the tubular epithelium was swollen and more granular than normal. This granulation, however, was not so prominent as after shorter periods of ligation. Tissue preserved in Fleming's solution showed no evidence of fatty change.

Ligation of Pedicle in the Rat. The method of procedure was the same as in the rabbit. One rat was killed after sixty-nine days and two after forty-four days had elapsed. The effects in these animals did not differ from those in the rabbits. The urine showed occasional albuminuria, but never casts or blood. The opposite kidney was always enlarged, but histologically no change except an increased granulation of the cells was found.

It will be seen from the protocols given that ligation of the renal vessels causes a complete destruction of the ligated kidney, characterized by diminution in size, thickening of the capsule, and liquefactive necrosis. The remaining kidney is increased in size and histologically presents no changes except an increase in the cell granules, which are especially prominent in the earlier periods (ten days) of observation.

Control. *Simple Nephrectomy.* In the experiments previously described an attempt had been made to produce autolysins by causing one kidney to do the work of two and at the same time remove to the degenerative products of its fellow. Changes in such a kidney, if they occur, might conceivably, therefore, be due either to increased functional activity or to the action of the products of the destroyed

kidney, or to both of these influences combined. In order to determine with certainty the effect of increased activity alone, simple unilateral nephrectomy has been carried out by way of a control.

Rabbits. Four rabbits were subjected to simple unilateral nephrectomy. One died within twenty-four hours. The others were killed fifteen, forty-two, and eighty-eight days after the operation. The effects noted were identical with those of the ligation experiments—*i. e.*, loss of weight and slight intermittent albuminuria. The histologic examination of the kidneys showed in all but the last a marked increase in the granulation of the cells. This change was, however, absent from the eighty-eighth-day specimen, which, except for a closer arrangement of the tubules, could not be distinguished from normal specimens.

Nephrectomy in the Rat. In a similar series of experiments in the rat, the animals being killed thirty-nine, forty-four, and fifty-two days after the operation, the results were identical with those described in the rabbit, the cells of the cortical tubules showing an increased granulation.

Summary. Ligature of the ureter or vessels of one kidney does not produce changes which differ in any way from those which follow unilateral nephrectomy. Four changes occur: loss of weight, slight intermittent albuminuria, and hyperplasia of the opposite kidney associated with, as a rule, increased granulation of renal cells. In examining into the causes of the changes mentioned we must consider first the increased function of the remaining kidney, a condition common to all three methods of experimentation, and, second, the elimination by the remaining kidney of the products of the destruction of the ligated kidney. If the products of the latter are directly injurious we should expect graver changes in the opposite kidney than in the instance of the nephrectomized animals. As such is not the case, we are forced to the conclusion that increased function is responsible for the changes observed in all three series, and that the products of the dissolution of one kidney exert no directly deleterious action on the opposite kidney. In other words, under normal physiologic conditions, degeneration of renal cells does not lead to the production of autonephrotoxins.

ON THE PRODUCTION OF ISONEPHROTOXINS.

Isonephrotoxins, theoretically, are produced by injecting the kidney of one animal into another animal of the same species. The blood serum of animals in which attempts have been made to generate autonephrotoxins has been considered, when introduced into another animal of the same species, as isonephrotoxic. The following methods of producing an isonephrotoxic serum have been employed:

(*a*) Unilateral ligation of the ureter.

(*b*) Unilateral ligation of the renal vessels.

(*c*) Immunization of animal against kidney of animal of same species.

Serum of Animal with Ligated Ureter. Néfédieff was the first to attempt the production of an isonephrotoxic serum by the ligation of the ureter in the rabbit. Serum obtained from these animals twenty-one and forty-one days after the ligation, when infused in a dose of 4 c.c. per kilo, produced, according to him, albuminuria and loss of weight. The histologic study of the kidney in one animal revealed destruction of the tubular epithelium, the presence of casts, and a moderate "round-cell" infiltration. Ascoli and Figari report similar results, while Albarran and Bernard obtained one positive result in eight animals which they injected.

My conclusions are based on five observations. The doses and periods elapsing before the animals were killed are given in the following table. The injection of serum into the rabbits was made into the marginal ear vein.

Rabbit with ligated ureter.	Bled on	Injected animal.	Dose.[1]	Killed on	Result.
Rabbit 10	67th day	Rabbit 29	1–352	7th day	Transient albuminuria negative
" 10	89th "	" 48	1–165	7th "	
" 52	22d "	" 60	1–130	6th "	
" 57	20th "	" 61	1–284	3d "	
" 57	42d "	" 71	1–200	2d "	

In four of the experiments the injection of the serum produced no appreciable effect. No change occurred in the weight of the animal,

[1] This method of indicating the dose refers to the relation between the amount of serum injected and the weight of the animal. Thus Rabbit 71 weighed 2000 grams and received 10 c.c. of serum, or 1 c.c. to 200 grams of body weight.

the examination of the urine was negative, and the histologic examination of the kidney revealed no changes. Rabbit 29, however, lost 20 grams in weight and exhibited a slight trace of albumin for two days following the injection. In this animal the kidney presented changes of cloudy swelling, but none of those said by Néfédieff to be characteristic of cytolysis. The fact that Rabbit 48 received later a much larger dose of the same serum with no effect suggests that some accidental circumstance accounts for the result in Rabbit 29, and, as will be shown later, the injection of normal rabbit's serum will sometimes produce an evanescent albuminuria.

A similar set of experiments upon the rat gave negative results.

An illustrative protocol is appended:

Rabbit 48. February 17th, isolated. Weight, 1320 grams. February 18th and 19th, examination of urine negative. February 19th, received 8 c.c. of serum of Rabbit 10 (ureter ligated 89 days) in marginal ear vein. No ill effect. February 20th to 25th, urine normal. February 26th, weight 1360 grams; killed; all organs normal; cultures from heart's blood sterile. Histologic examination of the kidney showed it to be normal.

Ligation of Vessels. As far as I am aware no tests have been made of the isonephrotoxic action of the serum of an animal with unilateral ligation of the renal vessels. Such a serum should, theoretically, contain the products of a rapid, complete destruction of the kidney substance. Experiments with such a serum are tabulated below:

Rabbit with ligated vessels.	Bled on	Injected animal.	Dose.	Killed on	Result.
Rabbit 11	65th day	Rabbit 34	1–170	7th day	Negative
" 11	87th "	" 50	1–100	5th "	"
" 58	21st "	" 63	1–200	4th "	Faint trace of albumin on second day
" 59	23d "	" 64	1–300	3d "	Negative
" 58	44th "	" 70	1–190	3d "	"
" 58	44th "	" 72	1–130	2d "	"
" 59	48th "	" 73	1–130	3d "	"

In all but one of these animals the weight remained practically unchanged, and albuminuria did not occur; and in all the kidneys upon histologic examination appeared normal. The same results were obtained with the rat.

Unilateral Nephrectomy. As control experiments for the above series I have utilized the serum of the rabbit and rat in which one kidney had been removed. Ascoli and Figari have claimed that the serum of nephrectomized animals produces albuminuria when injected into other animals of the same species.

Although I have administered doses as high as 1 : 150 of the body weight, I have not been able to produce in any animal albuminuria, and upon histologic study I have failed to find any pathologic change in the kidney. As I will show later, a more satisfactory explanation of Ascoli and Figari's result is offered by the fact that normal rabbit's serum causes rarely a transient albuminuria when introduced into another animal of the same species.

Serum Produced by Injecting the Rabbit's Kidney into the Rabbit. According to Castaigne and Rathery, the injection into the rabbit of a serum obtained in this way causes cytolytic changes in the renal epithelium. In repeating this experiment I injected rabbits four or five times, at intervals of seven to ten days, with amounts of rabbit's kidney varying from one-third of a kidney to the entire organ. The following table summarizes this experiment:

Immunized animal.	Number of kidney injections.	Bled after injection.	Animal receiving serum.	Dose.	Killed on	Result.
Rabbit 4	1	1st	Rabbit 9	1–400	4th day	Trace of albumin on 2d and 3d days
" 13	5	3d	" 23	1–335	9th "	Negative
" 13	5	5th	" 43	1–100	5th "	"
" 18	5	5th	" 44	1–200	4th "	"
" 19	4	4th	" 41	1–360	11th "	"

As this table shows, in all but the first animal no effect was produced. The histologic examination of the kidneys was uniformly negative.

The protocols which follow show the mode of carrying out this set of experiments.

Rabbit 13. Received the following injections of rabbit kidney in the peritoneal cavity: November 21st, two-thirds of a kidney; December 3d, one-third of a kidney: December 18th, one-half of a kidney; January 19th and February 5th, an entire kidney. It was bled on January 6th and February 11th. The serum from the first bleeding was used for Rabbit 23, and from the second for Rabbit 43.

Rabbit 23. January 6th, isolated. January 7th, urine normal. Weight 2170 grams; received in the marginal ear vein 6.5 c.c. of serum of Rabbit 13; no ill effect. January 8th to 14th, no albuminuria; sediment, negative. January 16th, weight 2196 grams; killed; all organs normal in appearance.

Rabbit 43. February 11th, isolated. February 12th, weight 1655 grams; no albumin in urine; received in marginal ear vein 16 c.c. serum of Rabbit 13. No ill effect. February 13th to 17th, no albuminuria; sediment, negative. Weight, 1650 grams; killed; postmortem examination reveals edema of subcutaneous tissues of abdomen and slight amount of clear fluid in peritoneal cavity. Uterus enlarged and contains blood-stained fluid, and dead but not macerated fetuses. Kidneys, pale; other organs negative.

Although I have failed by the several methods given in demonstrating isonephrotoxins, it has been pointed out that occasionally slight traces of albumin appeared in the urine of the injected animals. This albuminuria has, however, always been evanescent and unaccompanied by changes in the renal parenchyma. In order to determine whether or not normal rabbit's serum is capable of setting up this condition I have performed the following control experiments:

Rabbit 20. December 18th, isolated; weight, 2720 grams. December 19th, no albuminuria; 7 c.c. of normal rabbit's serum injected into marginal ear vein. December 20th, no urine. December 21st, 72 c.c. of high-colored urine; distinct trace of albumin; sediment, negative. December 22d, no urine. December 23d and 24th, faint trace of albumin. December 25th and 26th, no albumin. December 27th, killed; weight, 2715 grams. Kidneys: on section, cortex pale; pyramids injected; other organs normal; urine from bladder contains no albumin.

Rabbit 21. December 31st, isolated; weight, 1520 grams. January 1st, no albuminuria; 3.5 c.c. of normal rabbit's serum injected in ear vein. January 2d to 12th, urine free from albumin. Killed on January 12th; weight, 1510 grams; organs normal.

Rabbit 28. January 17th, isolated; weight, 1575 grams. January 18th to 21st, no albuminuria. January 23d, no albumin; received 8 c.c. normal rabbit's serum in marginal ear vein; weight, 1572 grams. January 24th, no urine (distended bladder can be palpated). January 25th, 26th, and 27th, faint trace of albumin. February 1st, killed; weight, 1540 grams; organs normal.

Thus in two of three instances albumin has appeared in the urine as the result of injecting normal rabbit's serum. These results are in accord with those of Weiss, who found that rabbit's serum injected into a rabbit may produce albuminuria, especially if the animal injected is of the opposite sex. At the time of my experiments I was

not acquainted with this fact, and made no note of the sex of the animals. The results of these controls indicate, however, that the serum injections may account for the effects observed after the injection of various serums supposed to be isonephrotoxic. It seems warrantable, therefore, to conclude that it is impossible by the several methods described to produce isonephrotoxins.

ON THE PRODUCTION OF HETERONEPHROTOXINS.

Heteronephrotoxins, prepared by injecting one animal with the kidney of another of a different species, have been made by Lindemann, Nefedieff, Castaigne and Rathery, Ascoli and Figari, and Bierry. Rabbits and guinea-pigs have been used by all investigators except Ascoli and Figari and Bierry, who employed the rabbit and dog. The method of immunization is identical with that already given, and consists in injecting an animal of one species three or four times, at intervals of seven to ten days, with the kidney of another species of animal. The serum is obtained in the manner already described and introduced in any desired amount into an animal of the species which furnished the kidney used for immunization. The injections of heteronephrotoxic serum give rise, in the experience of the above investigators, to albuminuria, progressive emaciation, and death in from three to twenty days. The kidneys themselves show various grades of degenerative changes, consisting of diminution and disappearance of cell granules, necrosis of cells, accumulation of round cells, and collection of granular material and casts in the tubules. Some of the authors have also described symptoms which they consider to agree with those caused by uræmia in man.

There are some discordant results. For example, Schultze, who employed the rabbit and guinea-pig, obtained wholly negative effects, and Albarran and Bernard thought that they proved that, while the serum may produce albuminuria, the action is not specific.

In my experiments the following procedures were employed:

(1) The injection of the kidney of the rabbit into the guinea-pig.

(2) The injection of the kidney of the guinea-pig into the rabbit.

(3) The injection of the kidney of the dog into the rabbit.

The serum produced by the first two methods gave unsatisfactory and inconclusive results. That portion of the work will, therefore,

be discussed briefly, after which I will turn to the third method, which has yielded results of much interest.

Guinea-pigs were injected into the peritoneal cavity at intervals of seven to ten days with rabbit's kidney. The amount of kidney injected at each sitting varied from one-third of to an entire organ. The guinea-pig was bled from the carotid artery one week to ten days after the last injection and the serum injected into the ear vein of rabbits in doses of 1 : 300 of the body weight. Four rabbits were injected practically with negative results. In one of these a slight trace of albumin appeared on the second day, and in another on the fourth day. In neither, however, was it persistent, and none of the animals lost in weight. The four rabbits were killed from five to seven days after the injections and the kidneys studied without discovering any lesions. The following protocol is an example :

Rabbit 45. February 12th, isolated. February 13th, urine normal; weight, 2097 grams. February 14th, urine normal; received in marginal ear vein 7 c.c. of serum of Guinea-pig 10 (having received three injections of rabbit's kidney). February 15th, no albuminuria. February 16th, faint trace of albumin; sediment, negative. February 17th to 19th, no albuminuria. Rabbit killed on 19th; organs normal.

Two control rabbits received the same doses of normal guinea-pig's serum; in one no effect was discovered; in the other a slight trace of albumin appeared in the urine on the fourth day. The kidneys were normal.

Reversing the treatment, rabbits received, at intervals of a week or ten days, three or more injections of guinea-pig's kidney, using at each sitting two organs. The serum of these animals was injected into the peritoneal cavity of guinea-pigs in the dose of 1 : 150 to 1 : 40. Nine experiments were made, as is shown in the following table :

Guinea-pig.	Dose.	Duration.	Result.
21	1–110	Twenty days; killed	Loss in weight; urine normal; kidney normal
27	1–40	Twenty-four hours; died	Peritonitis; urine normal; *excluded.*
28	1–100	Twenty-four hours; died	" " "
29	1–100	Forty-eight hours; died	" " "
30	1–80	Twenty-four hours; died	" " "
31	1–133	Forty-eight hours; killed	Loss of weight; urine normal; kidney normal
32	1–150	Five days; killed	" " "
33	1–130	Six days; killed	Loss of weight; urine normal; trace of albumin second day: kidney normal.
34	1–100	Four days; killed	Loss of weight; urine normal.

It is at once apparent that these results differ entirely from those of the investigators who report positive effects. The marked toxicity which they have described I have not observed. The only animals which succumbed within a few days after injection were those in which the peritoneum had been infected. In all of the latter, in spite of normal urine, the kidneys showed moderate degenerative lesions of the type of cloudy swelling.

In the remaining five animals the only constant effect was a loss in weight varying from one-tenth to one-eighth of the body weight; and, also, contrary to the experience of the French writers, albumin was found in the urine of but one of the guinea-pigs, and then for one day only, and no lesions were detected in the kidneys upon histologic examination.

The control experiments with normal rabbit's serum were practically negative in regard to the occurrence of albuminuria and histologic changes in the kidney. In but one of eight controls was albumin found in the urine. The same loss of weight, however, took place. As rabbit's serum is hemolytic for guinea-pig's corpuscles it seems not improbable that this property alone may be responsible for the occasional albuminuria and the loss in weight.

Heteronephrotoxins Produced by Injecting the Dog's Kidney into the Rabbit. By this procedure powerful heteronephrotoxins have been obtained by Bierry and Ascoli and Figari. These authors would seem to have fallen into an error which has not been alluded to and which must be taken into account. Ascoli and Figari have noted, among the effects of the injections of this serum, albuminuria, hematuria, and the occurrence of tube casts. While all these effects are conceivably due to the action of a nephrotoxin, it is worth while inquiring whether any of them could be the result of the action of hemolysins.

The constant occurrence of hemoglobinuria in my early experiments led me to test the hemolytic power of the serum, and I ascertained that it was strongly lytic for dog's corpuscles *in vitro*. As normal rabbit's serum has no destructive action on dog's blood, the hemolysis could be explained on the assumption that a sufficient amount of blood had been introduced with the kidney emulsion to bring about the formation of an hemolysin. The urine of animals treated with this nephrotoxin showed albuminuria, hemoglobin; finely granu-

lar, epithelial, and fatty casts; and the albumin persisted after the hemoglobin had disappeared.

Starting with the knowledge that the nephrotoxic serum was strongly hemolytic, it was obviously impossible to decide to what extent the renal disturbance was due to the hemolytic and to what extent to the nephrotoxic action of the serum. It is a well-known fact that the elimination of hemoglobin by the kidneys sets up degenerative changes in the renal epithelium. In order to determine the effects upon the kidney of the nephrotoxin on the one hand, and the hemolysin on the other, another series of experiments was performed. One group of rabbits was injected with dog's red blood corpuscles and another group with dog's kidney from which all blood had been washed by the injection through the arteries of salt solution. Serum from the former produced, when introduced into the veins of dogs in the proper dose, hemoglobinuria, which disappeared in a few days, leaving the urine practically normal. Casts were found not at all or only in small numbers. Serum from the animals treated with washed kidney failed to produce hemoglobinuria, but set up an intense albuminuria with numerous casts, both persisting for many days.

Through the use, therefore, of a method of analysis a nephrotoxin free from hemolysin has been obtained. Ascoli and Figari do not give the details of a microscopic examination of the sediment in their dogs, but my experience has taught me that the hematuria which they describe is really a hemoglobinuria. I have never found red corpuscles in the urine of animals treated with serum prepared from the washed kidney, from which I have concluded that nephrotoxic nephritis in the dog is unassociated with free hemorrhage from the kidney.

Serum from Unwashed Kidney. In these experiments the amount of dog's kidney employed at each injection was about eight grams, but varied from four to twelve grams. The rabbits were bled seven to ten days after the third injection. The serum inoculations were made in the saphenous or femoral veins of the dog in doses of 1 : 900 to 1 : 300. Five dogs were injected with practically identical effects. The observed phenomena are the following : Within eighteen to twenty-four hours a large quantity of dark red urine is voided, albumin in large amount occurs, and the sediment contains hemoglobin in granules, clumps, or solid tube casts. In the course of the next three to five days the hemoglobin has disappeared, although

biliary pigments have appeared. Definite casts occur usually on the second or third day, the finely granular variety predominating, although fatty and epithelial forms are also abundant; the hyaline form of casts rarely appears.

For the first four or five days albumin is present in large amount, it then gradually diminishes, disappearing, as do the casts, also, after ten to fourteen days. The persistence of albumin for two or three months, as described by Ascoli and Figari, I have never observed.

The kidneys are swollen, edematous, and paler than normal. On section, an extensive fatty change is indicated by the pale yellow tint of the boundary zone and the cortex, which is irregularly mottled. An intense injection of the glomeruli is not uncommon. Upon histologic examination the lesions are: extensive granular degeneration of the convoluted tubules and a fatty metamorphosis limited almost exclusively to the loops of Henle. The lumen of the tubules contain granular material and many hyaline and granular casts. Of the latter the greater number are found in the collecting tubules. The glomeruli are intensely congested, and coagulated serum and coarse granular particles distend the capsular space; lesions within the tuft itself are sometimes observed. The lymphatics of the organ are often distended by serum. A loss in weight of the animal takes place.

Dog 3. Weight, 6540 grams. February 9th, isolated. February 10th, urine normal. Received at 3 P.M. in femoral vein, under ether anesthesia, 15 c.c. serum of Rabbit 16.[1] February 11th at 9 P.M., no urine; animal drowsy, stupid, respiration quickened; 4 P.M., 174 c.c. of dark reddish-black urine with acid reaction. Filtered and diluted 1 : 5 gives almost instantaneous, dense, solid, albumin ring. Sediment: much yellowish granular material, which clears up on addition of acetic acid, leaving yellow hyaline droplets, varying in size, but smaller than red blood corpuscles. Neither red blood corpuscles nor "shadows" present; few round and oval cells, more or less granular, apparently renal cells; no casts. February 12th, 9 A.M., same general condition. Urine, 162 c.c., dark red in color; by spectroscope filtered urine gives methemoglobin band. Dense albumin ring in dilution 1 : 10. Sediment: yellowish, globular material greatly increased and occurring in masses, sometimes in cylinders; few fine granular casts, and granular cells often arranged as casts; no blood corpuscles. February 13th, condi-

[1] Rabbit 16 had received four injections of dog's kidney in the peritoneal cavity. Its serum was strongly agglutinative for dog's corpuscles, and caused complete hemolysis in ten minutes, in the proportion of nineteen parts of serum to one of red cells.

tion greatly improved. Urine, 150 c.c., of yellowish-red color, and containing a large quantity of chocolate-colored sediment. Filtered urine is amber colored; fair ring of albumin by HNO_3. Gmelin's test for bile gives marked reaction. Sediment: large masses and cylinders of bright yellow pigment granules and globules; no red corpuscles; few renal cells and fine granular casts. February 14th, 420 c.c. of smoky, amber-colored, acid urine, containing much brownish sediment and a trace of albumin. Sediment: round and spindle-shaped epithelial cells, yellow pigment diminished; few fine granular casts; no red corpuscles. Bile test positive. February 15th, 114 c.c. amber-colored, smoky urine; faint trace of albumin; bile present. Sediment: yellowish pigment in large amount; few renal cells and finely granular casts; no red corpuscles. February 15th, 180 c.c. urine, light yellow color; dense ring of albumin; bile present. Sediment: yellow pigment; few cells and finely granular casts. February 17th, general condition good; killed at 2 P.M.; weight, 6250 grams. Corresponding to injection site, clean ulcer of the leg; kidneys pale, swollen, edematous; capsule peels readily, leaving surface smooth. Cut surface pale, with distinct yellow color of boundary zone and lower portion of cortex. Glomeruli pale and prominent. In the bladder, 40 c.c. urine, of dark amber color, containing sediment of small, brownish granules; dense ring of albumin; bile present. Sediment: made up of bright, golden, globular pigment, occurring in small granules and globules; many granular renal cells and finely and coarsely granular casts; no blood corpuscles.

Histologic Examination of Kidney. The cells of the convoluted tubules are granular, swollen, and stain feebly; those of the loops of Henle are vacuolated, and in osmic preparations are seen to have contained much fat. This fatty change is limited practically to the loops of Henle. The lumina of the cortical tubules contain much granular material, which appears to be coagulated albumin, and bright, eosin-staining material, probably of hemoglobin origin. The cortical tubules contain few, the straight tubules many hyaline and granular casts. The glomerular tufts are unchanged, but the capsular spaces frequently contain coagulated serum.

As a part of the study an effort was made to demonstrate the dual activity of the serum by separating the hemolytic and nephrotoxic constituents. To accomplish this the serum was treated for one hour with washed dog's corpuscles at zero temperature; the mixture was then centrifugalized, and the supernatant fluid separated and injected into the dog. The serum was faintly hemolytic *in vitro* and did not cause hemoglobinuria. The nephrotoxic power was, however, retained, although it had been reduced in strength. This reduction of the nephrotoxic power led me to treat a pure nephrotoxic serum—that is, one prepared with washed kidney—with red corpuscles, with the

result that its power to set up renal disturbance was also greatly diminished. From this the conclusion could be drawn that while the hemolytic and nephrotoxic constituents are largely distinct, yet red corpuscles can remove from a non-hemolytic serum part of its nephrotoxic content. This method of obtaining a pure nephrotoxin from a mixed serum was, therefore, abandoned, and the method of immunizing with washed kidney adopted.

Serum from Washed Kidney. In preparing the kidney for injection the blood was washed out with warm sterile salt solution before removing the organ from the animal. The kidney was protected by sterile gauze pads moistened with salt solution, and the aorta clamped above and below the origin of the renal artery, in order to prevent the escape of large amounts of blood over the field of operation. The aorta was then incised and a glass cannula connected with an irrigation apparatus was introduced into the orifice of the renal artery. As the renal artery of the dog divides almost immediately into two branches, this method of entering the artery obviated the use of two cannulæ. Occasionally, however, a kidney has two separate arteries, in which case a double cannula is used, or the single one is used first in one branch and then in the other. Although the pallor of the kidney and the clear appearance of the fluid leaving the vein are sufficient evidence of the complete removal of the blood, confirmation of this was obtained by histologic examination of the kidney. The washed organ is injected in the same manner as the unwashed kidney. The serum of the rabbit receiving it is agglutinative *in vitro*, but not at all or only faintly hemolytic for dog's corpuscles. It never produced hemoglobinuria when injected into dogs. On the other hand, it has a powerful nephrotoxic action, as is indicated by the severe albuminuria and cast excretion which it induces. The casts are finely granular and less frequently fatty, epithelial, and hyaline. Granular and fatty renal cells are generally abundant. The casts appear usually within twenty-four hours, and disappear in twelve to fifteen days. Albumin in faint traces may persist for longer periods. In all animals a remarkable loss of weight occurred. Histologically, the lesions due to this serum resemble, to a marked extent, those met with in animals treated with a serum prepared from the unwashed kidney. The two differ chiefly in the absence of all evidence of blood destruction in the one as compared with the other. Distinct changes

in the glomerular tuft have been met with. A most striking one consists of the occurrence of fine hyaline thrombi in the glomerular capillaries with associated degeneration and fusion of neighboring endothelial cells. The structure and general arrangement of these thrombi suggest the agglutinated red blood corpuscle thrombi recently described and explained by Dr. Flexner.[1]

The above observations are based on ten experiments. The injections were made into the saphenous or femoral veins in doses of 1 : 1600 to 1 : 500. No definite relation between the amount of serum injected and the severity of the reaction was established.

Dog 14. March 26th, isolated; weight, 6340 grams. March 27th to 30th, no albuminuria; sediment negative. March 30th, received 10 c.c. of serum of Rabbit 54[2] in internal saphenous vein; light ether anesthesia. April 1st, 130 c.c. light amber urine; slight alkaline reaction; much albumin by heat and HNO_3. Sediment: few epithelial cells; no casts or red blood cells. April 2d, 114 c.c. high-colored, smoky urine; slight alkaline reaction; no hemoglobin; no bile. Much albumin by heat and HNO_3. Sediment: hyaline and finely granular casts with adherent fat and epithelial cells; fine renal and bladder cells; no red blood corpuscles. April 3d, 44 c.c. high-colored, smoky urine; dense ring of albumin. Sediment: much renal and bladder epithelium: hyaline and finely granular casts with fat; no red corpuscles. April 4th, 104 c.c. high-colored, smoky urine; alkaline reaction; dense ring of albumin. Sediment: as on the 3d; weight, 5840 grams. Killed at 3 P.M.; kidneys swollen; capsule slightly adherent to kidney substance; on section, edematous, pale yellow in color; glomeruli distinct but pale; a few punctiform hemorrhages beneath the capsule and in the cortex; other organs normal; urine from bladder of light yellow color, acid; dense ring of albumin. Sediment: after centrifugalization, many hyaline, finely granular, fatty, and epithelial casts and renal cells; no red corpuscles; bile test negative.

Histologic Examination of Kidney. The cells of the convoluted tubules are swollen and highly granular; they stain feebly. The cells of the loops of Henle are granular and vacuolated. In osmic acid preparations fat droplets

[1] In the study of this condition it was found that the thrombi stained by Weigert's fibrin stain. This, however, does not prove that they are composed of fibrin, for red blood corpuscles, especially after Zenker's hardening, often give this staining reaction, and definite corpuscles reacting in this way were seen in the same section. A more detailed histologic study will appear later in a supplementary communication.

[2] Rabbit No. 54 had received into the peritoneal cavity on March 5th, 14th, and 21st, each eight grams of dog's washed kidney. It was bled on March 29th. The serum was agglutinative for dog's corpuscles, but not hemolytic after six hours in the proportion of one part of corpuscles to nineteen parts of serum.

are numerous and are limited to the cells of these tubules; in the lumina granular material and casts are found. The latter are hyaline, granular, and epithelial in kind, and are especially numerous in the collecting tubules. The capsular space of the glomeruli show slight accumulations of serum, and now and then an irregular mass of fibrin. The capillaries of the tufts contain not infrequently hyaline thrombi, which react to Weigert's fibrin stain in the same manner as the fibrin in the capsular spaces: the hyaline tubular casts take at times the stain. The cells of the capillaries are more or less fused together and show fragmented nuclei about the thrombi.

Nephrotoxic Action of the Serum of Dogs Injected with Heteronephrotoxic Serum. Bierry found that the serum of dogs in which a renal disturbance was set up by the injection of a heteronephrotoxic serum possessed the power, when introduced into a second dog, of causing changes in the kidney similar to those produced in the first dog. This experiment was suggested by the observation of Lindemann that the serum of dogs suffering from nephritis induced by the administration of potassium bichromate would cause similar lesions when injected into the circulation of normal dogs. I have repeated the experiments as conducted by Bierry and have been able to excite in two of four dogs a mild but transient renal disturbance, indicated by the excretion of traces of albumin and a few finely granular casts. In one of the successful experiments the albumin and casts disappeared on the fourth day, and in the two experiments classed as negative one dog exhibited traces of albumin on the third day, but no casts were present, and the other was absolutely negative. At the postmortem examination of the kidneys in each of the positive cases the boundary zone and lower cortex of the organ presented the grayish-yellow color which I have described several times, and which is associated with fatty changes in Henle's loops. The microscopic examination of the kidneys confirmed the findings in the other cases.

Although I have not produced as severe lesions as did Bierry, the milder renal disturbance which I observed is confirmatory of his experiments. It is, moreover, only fair to state that the doses used in my experiments were smaller than those which Bierry employed. The largest dose given by me was 1 : 335, while his dose was almost twice as great as this. The negative experiments in my hands were those in which the serum was obtained from dogs which had received but one injection of heteronephrolytic serum, while the positive cases

came from dogs which had received four injections of such a serum within a period of nine weeks.

Heated Nephrotoxic Serum. Nephrotoxic serum prepared by injecting washed dog's kidney into the rabbit is still active after heating to 56° C. for half an hour, and its inoculation in doses of 1 : 900 gives rise to albuminuria and cast excretion. The gross microscopic changes in the kidneys are identical with those produced by unheated serum.

Heteronephrotoxic Serum Prepared from Renal Cortex and Medulla Separately. In all the experiments thus far considered the entire kidney was injected in producing the active serum. It was considered worth while to determine whether any difference of toxicity might occur if the two parts of the organ were used separately. Two rabbits were, therefore, treated with washed cortex (7 to 9 grams at each injection) and a third rabbit with washed medulla of the kidney. Of the two rabbits treated with the cortex one developed a serum which produced effects in no way to be distinguished from those described in the previous pages; but the other yielded a serum which caused almost immediately fatal results. Three dogs receiving intravenously the latter serum in doses 1 : 1000, 1 : 2000, and 1 : 3000, respectively, died almost instantly. The postmortem examinations, including the study of the brain, yielded no discoverable cause of death. Aside from intense congestion of the viscera nothing was found. This serum was, it may be mentioned, slightly hemolytic; but the action cannot be explained on the basis of this property, as hemolytic serum in such small doses does not cause rapid death. The serum introduced into the peritoneal cavity in the dose of 1 : 1500 in a fourth animal set up a condition of stupor with embarrassment of the heart's action and the respiration, from which the animal partially recovered after ten hours, the condition of depression continuing for two days. A fifth animal was given 1 : 1800 subcutaneously, and, while it failed to develop general symptoms, a moderate albuminuria with cast excretion occurred.

The serum of the rabbit treated with the medulla was given intravenously in doses of 1 : 1100 and 1 : 780 to two dogs, with the effect of causing a mild disturbance of the kidneys; slight albuminuria and cast excretions followed the injections. The microscopic examination of the kidneys showed a moderate granular and fatty degeneration of the epithelium with the presence of a small number of tube casts.

The outcome of the experiments with nephrotoxic serum prepared respectively from cortex and medulla is valuable as establishing the greater toxicity of the former, a fact in keeping with the difference in number and character of the renal cells contained within these anatomically distinct structures. That the more cellular and highly differentiated cortex should yield a more toxic serum than the more indifferently organized medulla is quite in keeping with the predictions.

Hemolytic Serum. The action of this serum upon the kidney was used as a control for that prepared with unwashed kidney. Incidentally the effect of repeated injections of the serum was studied with special reference to the production of permanent injury to the kidneys.

Rabbits were given three or four injections of 5 to 10 c.c. each of dog's blood at intervals of seven to ten days, which method yielded a serum strongly hemolytic for dog's blood corpuscles. The serum was employed intravenously.

The effect of the serum varied with the dosage. In amounts of 1 : 600 to 1 : 400 death took place in from three to ten hours. Post-mortem examination of dogs poisoned in this way show the blood to be laked and soft, gelatinous clots to be present in the heart and large vessels. The internal organs are congested and of a bluish-black color, the serous cavities contain a small amount of blood-stained, thin fluid, and the kidneys are swollen, edematous, and congested. The last organs, when sectioned, show the peripheral cortex to be of a dark red, the boundary zone of a deep pink color, and the medulla pale. If the bladder contains urine it is of a dark claret color, rich in albumin, and containing a sediment composed of casts and coalesced masses of altered hemoglobin, along with granular and fatty renal cells.

The smaller doses of 1 : 1000 to 1 : 3000 are not fatal; but the injected dogs develop hemoglobinuria in eighteen to twenty-four hours, which condition persists for three to five days. After the disappearance of the hemoglobin the urine is still high-colored and deeply stained with bile pigments. A yellow, jaundiced condition of the conjunctiva, lasting several days, is a constant symptom. The albuminuria which accompanies the acute condition rapidly diminishes as the urine becomes clear of blood pigments, although it may be

detected by the heat test for many days. I followed it in one animal for three weeks. The urinary sediment contains the products of destruction of red corpuscles and many renal cells. Beginning on the second or third day, a few casts of the finely granular type are found, but not invariably.

During the first days much granular and finely globular yellow pigment, either free or attached to casts or even cast-like, occurs. But red corpuscles in any form have never been seen. The urine clears up and becomes normal at the expiration, at times, of five or six days.

The principal change shown by the kidney is a remarkably fatty condition limited almost entirely to the loops of Henle, but present to a slight degree in the convoluted tubules. Casts are usually absent, although they may occasionally be found in the sections. Glomerular changes are wholly absent, except in animals dying within a few hours, when the capsular spaces are filled with serum.

A considerable loss of weight occurred in all animals, and in one dog hemorrhages in the adrenals were found.

The following is a protocol of an experiment with hemolytic immune serum, the dog having been killed before the urine returned to normal.

Dog 17. Weight, 5000 grams. March 31st, isolated. April 1st and 2d, urine normal. Received in internal saphenous vein 6 c.c. immune serum of Rabbit 56; no immediate ill effect. April 3d, 130 c.c. of dark red urine, giving a dense albumin ring. The sediment contains renal cells, much yellow granular and globular material, but no red corpuscles or casts. April 4th, 120 c.c. hemoglobin containing urine, of acid reaction with albumin. No red corpuscles or casts were present. April 5th, killed by chloroform; weight, 4720 grams. Normal healing of wound in leg. Kidney: slight adhesion of capsule; surface smooth. Section: cortex pale, swollen, striæ yellowish; glomeruli normal; urine from bladder contains much albumin and hemoglobin, and still shows the pigment.

The microscopic examination of the kidney showed an intense fatty condition of the cells, limited almost entirely to the loops of Henle, and granular degeneration with more or less disintegration of the cells of the convoluted tubules. The larger vessels show the red blood corpuscles in a state of agglutination and partially disintegrated. Some of the tubular lumina contain granular masses of coagulated albumin, with admixture of hemoglobin derivatives, but no casts.

The effects of repeated injections of an hemolytic immune serum is shown in the next experiment.

Dog 42. Weight, 9030 grams. June 1st, isolated. June 2d to 4th, urine normal. Received in left femoral vein 3.5 c.c. immune serum of Rabbit 68. No immediate ill effect. June 5th, large quantity of brownish-red, highly albuminuric urine. The sediment was composed of coarse and fine, yellow, globular material and a few renal cells, but no casts or red corpuscles occurred. June 6th and 7th, urine unchanged. June 8th, urine high-colored, but the tint is changing; a distinct ring of albumin by nitric acid test. Sediment: some yellow globules and granules, and renal cells; no red corpuscles or casts; urine of normal appearance, but a trace of albumin and a few yellow globules persist. The urine remained about the same until June 14th, when a few finely granular casts appeared. Normal was reached on June 28th. June 30th, injected into femoral vein 3 c.c. of immune serum (Rabbit 69). July 1st, reddish-black urine, containing abundant albumin and yellow globules and granules, but no casts or red corpuscles. July 5th, urine normal except for trace of albumin. July 10th, injected 6 c.c. immune serum (Rabbit 68) into peritoneal cavity; no ill effect. Killed on 19th; weight, 7540 grams; kidneys appear normal. Upon microscopic examination a moderate granular degeneration only was found.

Effects on the Kidney of Hepatotoxic Serum. As it seemed desirable to control the action of the kidney serum by some other somatogenic cytolysin a hepatotoxic serum, so called, was prepared. The liver was freed from blood in the same way as was the kidney, and several doses of 8 to 10 grams each were injected into the peritoneal cavity of rabbits. Two dogs received this serum into the saphenous vein in doses of 1 : 770 and 1 : 1000, respectively. Each developed albuminuria equal to that following the injection of "washed kidney" serum. In one casts were not found; in the other they were abundant. A protocol is given.

Dog 61. Weight, 14,060 grams. July 12th to 14th, urine normal; 14th, 15 c.c. of serum of Rabbit 86 were injected intravenously. July 15th, urine of light color; albumin present in large amount; a few hyaline and fine granular casts in the sediment. July 16th and 17th, marked albuminuria; sediment contains large number of hyaline, granular, epithelial, and fatty casts, and renal cells, but no red corpuscles. July 18th, killed; weight, 11,100 grams. Kidneys swollen and edematous; capsule peels readily. On section, cortex pale yellow, glomeruli injected; minute hemorrhagic points occur.

The histologic examination of the kidney showed granular degeneration of the convoluted tubules and fatty change in the loops of Henle. The straight tubules especially contained casts and granular detritus.

Effects on the Dog's Kidney of Normal Rabbit's Serum. The injection of normal rabbit's serum in doses of 1 : 900, 1 : 600,

and 1 : 500 was without influence on the urine or the histologic structures of the kidney.

Spontaneous Nephritis in Dogs. As a matter of routine all animals used in the preceding experiments were isolated several days previous to injection, and the urine carefully examined for albumin and casts.

This procedure enabled me to discover, among sixty-four apparently normal dogs, thirteen in which a persistent albuminuria existed, eleven showing at the same time tube casts. This condition will be denominated spontaneous nephritis, although the term is, perhaps, not a good one. I have been able to find no references to it in the literature, and am entirely in the dark as to its cause. The only other pathologic conditions commonly found in the dogs were an infection of the intestine by *uncinaria caninis* and the urethritis or balanitis from which dogs so frequently suffer. Both these latter conditions occurred with equal frequency in dogs with and free of renal disease. As the dogs were of the type of homeless animals picked up on the street, it is possible that the nephritis was set up by chemical poisons intentionally or otherwise administered. The kidneys and blood of several of the animals presenting albuminuria and cast excretion were examined bacteriologically with negative results. Protozoan infection could not be demonstrated in the blood histologically. The urine was studied during periods varying from three days to three weeks, and in one instance only (after ten days) did the urine return to normal. The albumin varied in different dogs and often in the same animal at different times. It is present usually in large amount, but occasionally only in faint traces. The casts in most instances are numerous. The predominating ones are finely granular, with less frequently fatty, epithelial, and hyaline varieties. The urinary sediment contains in addition fluctuating numbers of renal cells, and occasionally fine, feathery, yellow pigment, while red corpuscles are not uncommon. The histologic changes in the kidney consist of a granular degeneration and fatty metamorphosis of the parenchymatous cells, with numerous discrete interstitial foci of lymphoid and plasma cells, a condition suggesting the acute interstitial nephritis occuring in scarlet fever and diphtheria. In not all cases were the degenerative changes of the epithelium demonstrable. The collecting tubules frequently contain casts; the glomeruli show no change. The kidney appears swollen,

though seldom distinctly edematous; the capsule may or may not be adherent; the cut surface is grayish-yellow in color and often mottled with small, grayish, tubercle-like areas, and dotted by injected glomeruli. Hemorrhages are uncommon.

NEPHROTOXIC ACTION OF THE SERUM OF DOGS WITH SPONTANEOUS NEPHRITIS.

The preceding observations on the spontaneous nephritis of the dog may be of interest as a contribution to our knowledge of the pathologic conditions affecting this animal. The chief importance, however, for my purposes lay in the opportunity which was afforded of determining whether or not the serum under these circumstances is nephrotoxic when introduced into healthy dogs. As has been stated in the study of the heteronephrotoxins, Lindemann found that the serum of dogs suffering from a chemical (potassium bichromate) nephritis was capable of producing renal disturbance when injected into other dogs. Similar results with the serum of dogs which had received heteronephrotoxins were obtained by Bierry and confirmed by me.

Seven dogs with normal kidney functions were injected with the serum from animals with spontaneous nephritis, and in three a renal disturbance characterized by albuminuria and the excretion of casts, such as has been observed from the infusion of the serum of rabbits treated with washed kidney, occurred. In two moderate albuminuria, without cast excretion, resulted, while the remaining two gave negative results as far as the urine was concerned, although histologically in one fatty changes in the epithelium existed. In the character of the urine and the macroscopic and microscopic appearances of the kidney in the three examples of definite nephritis, these experiments agreed with those resulting from the injection of heterotoxic serum. The interstitial cell accumulations seen in the animals with spontaneous nephritis, being evidently a chronic condition, were not reproduced in the kidney of animals treated with the serum. The amount of serum injected varied from 1 : 600 to 1 : 400; the injections were made intravenously.

These experiments, although of the same general character as those reported by Lindemann and Bierry, are of perhaps greater interest because of the nature of the primary lesions. In endeavoring to

explain the results, either it must be considered that some exogenic toxic agent set up the renal lesions in the first dog, and was present in the animal's blood in such quantity that, when its serum was infused in the second animal in the proportion of 1 : 500 of the body-weight, it sufficed to produce marked disturbance of the renal function, such as is recognized in man as due to organic lesions, or that the degeneration of epithelium that may be assumed to exist in the first animal provoked a series of changes with the production of toxic substances active for a second animal.

The following combined protocols illustrate the production of renal lesions by the injection of the serum of animals with spontaneous nephritis, and the power of the serum of the second animal to set up similar disturbances in a third animal. It will be observed that the second injection of toxic serum has been controlled by a previous injection of normal dog's serum, with negative results.

Dog 22. Weight, 5520 grams. April 18th, urine highly colored, acid reaction, albumin by heat and nitric acid. Sediment: numerous finely granular and fatty casts, with occasional adherence of epithelial cells; free renal cells; no red corpuscles. April 20th and 21st, urine as on the 18th. On the 21st the dog was bled from the femoral artery and the serum injected into Dog 21.

Dog 21. Weight, 4580 grams. April 16th, urine normal; received 4 c.c. of normal rabbit's serum (as control for an experiment of a different nature). April 17th to 22d, daily examination of the urine negative. April 22d, received in internal saphenous vein 12 c.c. of serum from Dog 22. April 23d, 32 c.c. high-colored urine; highly albuminuric. Sediment: numerous finely granular and a few hyaline and epithelial casts; many granular cells, free fat and red corpuscles. April 24th, 22 c.c. of urine, smoky and high-colored; albumin in large amount; sediment as on the 23d. This condition persisted until May 1st, when the dog was bled. The serum thus obtained was injected into Dog 29 (see below).

Post-mortem Examination of Dog 21. Weight, 3520 grams. Wound of leg almost completely healed; abdomen contains about 400 c.c. of clear serous fluid.[1] Venous congestion of abdominal organs. Kidneys swollen and edematous; capsule peels readily; surface pale yellow in color, mottled, with

[1] This fluid contained no leucocytes and few endothelial cells; cultures were sterile. It resembled ascitic fluid. Whether or not it was the result of renal disturbance could not be determined. It has not been observed in other experiments. The associated venous congestion of the abdominal viscera points to a circulatory disturbance, but no lesions were found in the heart or vascular system aside from the operative obliteration of both femoral veins. These veins have been tied in several dogs without any ill effect.

minute hemorrhages; on section, appearance similar, with dull yellow boundary zone and pale medulla. Urine from bladder of high color; albuminous. Sediment: abundant, finely granular and fatty casts, and fatty renal cells. Upon histologic examination the kidney shows extensive granular and slighter fatty changes, besides which the tubules contain granular material and numerous finely granular casts.

Dog 29. Weight, 6110 grams. April 28th, no albumin by HNO_3; slight trace by heat.[1] Sediment negative. On 29th received 16 c.c. of normal dog's serum in femoral vein. April 30th to May 2d, no albumin; sediment normal. Injected in femoral vein 10 c.c. of serum of Dog 21. May 3d, urine albuminous, light in color. On microscopic examination numerous finely granular and fatty casts and renal cells. This condition of the urine continued until May 5th, when the dog was killed. The kidneys were swollen and injected: on section, the cortex was cloudy and of light yellow color. Microscopically they show a marked granular and slight fatty condition of the cortical tubules, and granular material, but no casts within the tubules.

ON THE PRODUCTION OF CHRONIC RENAL CHANGES.

None of the procedures described in the preceding pages have produced more than a temporary disturbance of the renal functions. The lesions, as indicated by the urine, have disappeared usually in from ten to fourteen days, rarely persisting for longer periods, and invariably returning to normal. In the hope that recurring disturbances might, by the production of more serious lesions which could not at once be repaired, lead to chronic renal changes repeated injections of heteronephrotoxic serum and of the serum of dogs with spontaneous nephritis were given. The following protocols give the results of these experiments:

Heteronephrotoxic Serum. Dog 18. Isolated April 3d; weight, 7170 grams. April 4th, urine normal. Injections were given as follows: April 5th, 12 c.c. in left femoral vein; urine returned to normal condition on April 15th; April 16th, 12 c.c. into the right femoral vein; urine returned practically to normal on May 14th, though occasional faint trace of albumin persisted until June 11th. June 14th, 4 c.c. into subcutaneous tissues (this serum intravenously was fatal in a dose of 1:3000); urine normal by June 18th. June 19th, 4 c.c. of the same serum in subcutaneous tissue; faint trace of albumin still present when animal was killed on June 29th. Each injection was followed

[1] Minute traces of albumin have occasionally been found where balanitis existed. In the absence of casts and other renal constituents the urine has been considered normal.

immediately by the excretion of albumin and casts, although the reactions after the third and fourth injections were less marked than after the first and second. This difference was evidently due to the smaller dose given subcutaneously. At autopsy the kidneys presented nothing that was noteworthy. Sections showed a granular degeneration of the cortical tubules and a slight fatty condition of the loops of Henle. A few hyaline casts were found in the collecting tubules. No other pathologic changes were present.

Serum of Dog with Spontaneous Nephritis. Dog 26. Isolated April 21st; weight, 6960 grams; urine normal. April 23d, 18 c.c. of serum were injected into the femoral vein. May 8th, urine still contains albumin and casts; received 12 c.c. of serum into the femoral vein. May 20th, trace of albumin persists, and a few casts are present; 20 c.c. of serum injected intraperitoneally; urine returned to normal on May 27th. May 30th, 20 c.c. of serum introduced into peritoneal cavity; albumin and casts still persist on June 2d, when 12 c.c. of serum were introduced into a superficial vein of the groin. Urine became normal on June 15th. On June 18th dog was killed. The kidneys in gross appearances were normal. On microscopic examination the only pathologic change consisted of a very few hyaline casts in the medullary tubules.

These attempts were futile in producing any but fleeting effects, and in the time and under the conditions dealt with nothing resembling chronic nephritis has been induced.

A STUDY OF THE BLOOD PRESSURE IN NEPHROTOXEMIA.

Ascoli and Figari ascribe the heart hypertrophy of nephritis to the action of nephrotoxins. Having observed what they considered to be an hypertrophy of the left side of the heart in a rabbit which had undergone unilateral ligation of the ureter, they undertook, by means of a kymographic study, to demonstrate a disturbance of the circulation as the result of the injection of heterotoxic serum. The changes which they describe, and which they consider to be due to a contracting influence exerted by the serum on the smaller vessels, are very indefinite. The kymographic tracings which they reproduce as showing the effect of the injection of 10 c.c. of heterotoxic rabbit's serum into the dog are difficult to reconcile with their theory of increased peripheral resistance. The tracing before injection is that of an abnormally low heart-beat and low arterial tension, the result of morphin narcosis. The injection of the normal serum resulted, in their hands, in a temporary change. The heterotoxic serum gives, according to them,

marked increase in the heart rate, with corresponding increase in the arterial tension; but nothing in the tracing indicates that the rise in tension is due to peripheral circulatory resistance, nor is the highest tension of much greater degree than that of the normal dog without morphin. The tracings fail to give a basis of measurement of absolute or negative blood pressure, and the text is silent on this subject.

In view of the importance of these observations careful controls seemed called for. I have, therefore, made kymographic tracings of rabbits receiving isotoxic serum, of dogs receiving heterotoxic serum, and of a dog in which the serum of spontaneous nephritis was injected. In all the experiments ether was used as the anesthetic, preceded in one instance by morphin.[1]

Dog 1. Control. Weight, 7450 grams. Morphin, 1.5 grains; ether; cannula in carotid artery; 5 c.c. normal rabbit's serum injected into jugular vein, followed in two minutes by a second dose of same amount. No effect except a slight drop in pressure at the time of introducing the needle, followed by immediate return to the normal level.

Dog 2. Weight, 5440 grams. Ether; cannula in carotid artery. Received 5 c.c. serum of Rabbit 16 ("unwashed kidney") in external jugular vein; no effect.

Dog 9. Weight, 6670 grams. Ether; cannula in carotid artery. Received 5 c.c. of serum of Rabbit 30 ("unwashed kidney") in femoral vein; slight temporary fall at the introduction of the needle, but immediate return to normal. After ten minutes a second injection with no effect. In order to demonstrate that this serum, although it produced no effect on the circulation, was nephrotoxic, the vessels were tied, wounds sutured, and the animal isolated. On the following day the examination was as follows: 34 c.c. dark claret-colored (hemoglobinuric) urine; dense ring of albumin by nitric acid. Sediment: numerous coarsely and finely granular casts, many granular and fatty renal cells; clump of yellow, globular pigment; no red corpuscles.

Dog 15. March 30th. Weight, 6500 grams. Ether; cannula in femoral artery. Received in opposite femoral vein (1) 5 c.c. of serum ("washed kidney") of Rabbit 54; slight transient drop with immediate return to normal level; (2) 5 c.c. of same serum after five minutes; same transient drop in pressure; (3) after two minutes 5 c.c. of normal salt solution at room temperature; drop in pressure slightly less in degree than after serum injection; (4) after four minutes 5 c.c. of serum of Rabbit 54; drop of same degree as after normal salt solution; (5) and (6) after three minutes two injections of iced normal salt solution at intervals of one and a half minutes; no effect;

[1] For the use of the apparatus and for invaluable assistance in conducting the experiments, I am indebted to Drs. C. C. Stewart and V. E. Henderson, of the physiological department.

(7) after three minutes 5 c.c. of normal rabbit's serum; same slight transient drop in pressure.

Dog 34. Weight, 6430 grams. Ether; cannula in femoral artery. Received in femoral vein 27 c.c. of serum of Dog 24 (spontaneous nephritis) in doses of 10, 10, and 7 c.c. at intervals of three minutes; no effect. Killed after sixteen minutes.

Rabbit 27. Weight, 1660 grams. Ether; cannula in carotid artery. Received (1) 5 c.c. of normal rabbit's serum in jugular vein; no effect; (2) 5 c.c. of serum of Rabbit 19 (treated with rabbit's kidney); respiratory and cardiac failure, with death in two minutes.

Autopsy. All organs negative; tracheal cannula plugged with mucus. In order to control this result, which was evidently an accident, the experiment was repeated.

Rabbit 40. Weight, 2180 grams. Ether; cannula in carotid artery; 5 c.c. of serum of Rabbit 19 injected into femoral vein; no effect after half an hour.

Rabbit 31. January 25th. Weight, 1830 grams. Ether; cannula in carotid artery; 7 c.c. of serum from Rabbit 18 (treated with rabbit's kidney) injected into external jugular vein; no effect after half an hour.

From these results the conclusion is warranted that the injection of nephrotoxic serum into rabbits and dogs produces no appreciable effect on the peripheral circulation, and Ascoli and Figari have been led into error by failure carefully to analyze their results.

ON THE TOXICITY OF RENAL PARENCHYMA.

Practically all investigators who have attempted to immunize animals against kidney substance have called attention to the high mortality among the animals, and have accounted for it by assuming that renal parenchyma is definitely toxic. When death takes place within a few days, or after two to three weeks, it is considered evidence of general toxic action. Besides this there has also been described what might be termed a local or specific toxic action upon the kidney, characterized by the excretion of albumin and associated with certain indefinite changes in the kidney cells. These latter changes Castaigne and Rathery describe as a diminution in or disappearance of the cell granules ("cytolyse protoplasmique"). This appearance they consider to be the specific effect produced by an injurious substance resulting from the disintegration of renal cells. The deficient granules, according to their interpretation, are, in part, washed out by

the urine constituting one of the substances recognized by tests for albumin, and, in part, absorbed when they appear in the blood as the nephrotoxic bodies. Similar cell changes have been described by Ramond and Hulot and also by Albarran and Bernard, who, however, regarded them as non-specific, since they appeared equally after injection of liver cells.

So firmly convinced have some writers been of the toxic action of kidney tissue that they have described what may be termed the lethal dose. Thus Castaigne and Rathery state that the introduction of two kidneys of the guinea-pig into the peritoneal cavity of the rabbit will cause death in two days, while one kidney causes a gradual weakening, emaciation, and death, the last being preceded by convulsions: and Albarran and Bernard state that two guinea-pig kidneys to 1000 grams of rabbit's weight are fatal in three days, and a somewhat smaller amount in four days.

In view of these opinions I paid special attention, in the course of my work, to the question of the toxicity of renal tissue, making note of any loss in weight, changes in the urine, and alteration in the histology of the kidney. Besides this I gave attention to the possibility that infection might play an important and neglected part, which led me to make routine bacteriologic examinations of all animals dying after the injections. No references to such examinations appear in the writings of previous investigators Another important control consisted of the injection of cells other than those of the kidney. The study of this phase of my subject embraced observations upon forty-one animals—rabbits receiving the kidney of the dog, guinea-pig, and rabbit, and guinea-pigs receiving the kidney of the rabbit, besides which liver cells and red corpuscles of the dog were injected into the rabbit.

The conclusions, which alone need to be given, at which I arrived were that practically all the deaths could be explained by bacterial infection of the peritoneum. The bacteria in a few instances came from accidental puncture of the intestine, and in the majority of cases were introduced with the injected material. The highest mortality from peritonitis was in guinea-pigs receiving rabbit's kidney, the lowest in rabbits receiving rabbit's kidney. In one of the animals only could the death not be explained on the basis of infection or accident. In view of these facts it seems justifiable to conclude that

the fatalities hitherto ascribed to the toxic action of the renal tissue are to be attributed to bacterial action.

The explanation of the slighter toxic action indicated by a loss of weight and the so-called specific kidney lesion receives illumination from the study of the effect upon the kidney of cells other than kidney cells. In all animals receiving cellular emulsions loss of weight and, not infrequently, slight intermittent albuminuria without cast excretion, occur. That there is nothing specific in this effect is shown by the identical action upon the kidneys of blood and liver cells.

In reference to the lesions of the renal epithelium described by Castaigne and Rathery I have examined the kidneys of seventeen animals. It was present in four of these: once in the rabbit injected with the kidney of the guinea-pig and three times in the rabbit which had received dog's kidney. The lesion is distinct and unmistakable for the absence of granules causes the lightly stained convoluted tubules to stand out sharply against the deeply stained tubules of the medulla. I found that besides the absence of granules in the protoplasm pyknotic changes in nuclei occur, and at times actual disintegration of the protoplasm has taken place. This series of changes can also be discovered after the injection of dog's blood and liver emulsion into the rabbit.

THE SPECIFICITY OF CYTOLYSINS.

I am led to make a note on this somewhat disputed question by reason of the correlative action of nephrotoxic and hemolytic serums. Von Dungern and Moxter produced cytolysins for ciliated epithelial and testicular cells, and found them to be hemolytic, on account of which they denied a strict specificity to the cytotoxins. Metchnikoff and Metalnikoff, on the other hand, believing in the specificity of the cytolysins, endeavored to explain the double action on the supposition that sufficient red corpuscles were injected with the epithelial cells to produce an hemolysin. Although Morgenroth has already discussed this conflicting question satisfactorily and drawn attention to the fact that specificity is a matter not of cells but of receptors, whence a given cell may be in chemical conformity with cells of a different organ or animal, I will add a word in support of that contention. Only recently Abbott has drawn attention to the strongly hemolytic prop-

erties of adrenal serum, which he also explains on the basis of identity of chemical or receptorial structure of blood corpuscles and adrenal cells.

So far as I am aware, in no previous experiments were organs washed free from blood employed for preparing the cytolysins. This I have done with the kidney and the liver, and I have controlled the washings microscopically so as to exclude all blood corpuscles. The heteronephrotoxic and hepatotoxic serums prepared in this way were still hemolytic, although to a less extent than the serum made from unwashed organs. As the hepatotoxin and hemolysin also exerted an action upon the renal function, an additional proof of the correlative action of these serums is at hand.

The conclusion is evident: besides the distinctions of receptor or chemical structure in these several kinds of cells, there are similarities of receptor organization, through which correspondences in those reaction-products, the cytolysins or cytotoxins, the results of immunization to cells, are brought about.

SUMMARY.

Autonephrotoxins in demonstrable quantities have not been produced by the several methods stated to lead to their formation.

Neither in the animals used for the purpose of producing autonephrotoxins, nor in others in which the same species of kidney was injected, could the formation of isonephrotoxins be demonstrated.

Very little success has attended the efforts to produce heteronephrotoxins through the reciprocal employment of rabbit and guinea-pig, while a powerfully nephrotoxic serum was yielded by the rabbit injected with dog's kidney.

The toxicity of a nephrotoxin is something apart from the destructive action of the serum hitherto employed upon the red corpuscles of the blood. To produce a nephrotoxic serum which shall have slight action only upon red corpuscles washed organs must be used.

Hemorrhage, other than punctiform extravasations into the renal substance, is not a result of nephrotoxic action. The effects hitherto described as due to hemorrhage have been the outcome of the destruction of red corpuscles and the elimination of hemoglobin by the kidneys.

In determining the injury inflicted by nephrotoxins upon the kidney parenchyma hemoglobinuria must be avoided. All the experiments upon heteronephrotoxic serum hitherto reported are not free from this source of error.

Owing to the prevalence of spontaneous nephritis among dogs, all experiments upon the renal functions of these animals should be carefully controlled by a previous study of the urine.

Hemolytic immune serum causes hemoglobinuria attended by a more transient disturbance of the renal functions, *e.g.*, albuminuria and cast-excretion, than that set up by nephrotoxic serum.

A nephrotoxic serum produced from renal cortex is more poisonous than one made from renal medulla.

Heating heteronephrotoxic serum from the rabbit to 56° C. for thirty minutes does not reduce its activity for the dog.

Hepatotoxic immune serum causes a marked disturbance of the renal function, which cannot be distinguished from the disturbance caused by nephrotoxic serum.

The histologic alterations produced by nephrotoxic serum consist of degenerations of the epithelia chiefly, with slighter and less uniform changes in the glomeruli. A striking effect is fatty metamorphosis of the cells of Henle's tubules. No changes of moment in the interstitial tissues were discovered.

Spontaneous nephritis in the dog occurs not uncommonly. The serum of dogs suffering from this condition is nephrotoxic even to the second remove for normal dogs.

The attempt to produce chronic renal lesions by repeated injections of nephrotoxic serum was unsuccessful.

The injection of heteronephrotoxic serum into dogs and of isonephrotoxic serum into rabbits was without immediate effect upon the blood pressure.

The correlative action of several kinds of serum upon different body cells was demonstrable, from which the conclusion that specificity is a function of receptors and not of cells in their entirety could be drawn.

Bibliography.

Abbott. Journal of Medical Research, 1903, ix., 329.

Albarran and Bernard. Archiv. de méd. expériment., 1903, xv., 13.

Ascoli and Figari. Berliner klin. Wochenschrift, 1902, xxxix., 561, 634.

Bertenson. Quoted by Albarran and Bernard.

Bierry. C. R. de l'Acad. des Sciences, 1901, cxxxii., 1145: C. R. Soc. de Biol., 1901, liii., 839.

Castaigne and Rathery. C. R. Soc. de Biol., 1901, liii., 1150: 1902, liv., 563: Archiv. de méd. expériment., 1902, xiv., 599; Presse Médicale, 1902, ix., 771: La Semaine Médicale, 1902, xxii., 273.

v. Dungern. Münch. med. Wochenschrift, 1899, xlvi., 1228.

Flexner. Univ. of Penna. Med. Bulletin, 1902, xv., 324.

Jordan. Transactions of the Chicago Pathological Society, 1902, v., 175.

Latapie. Ann. de l'Institut Pasteur, 1900, xiv., 106.

Lindemann. Centralblatt f. Allg. Path., 1900, xi., 308: Ann. de l'Institut Pasteur, 1900, xiv., 49.

Moxter. Deutsche med. Wochenschrift, 1900, xxvi., 61.

Metchnikoff. Ann. de l'Institut Pasteur, 1900, xiv., 1, 369.

Metalnikoff. Ann. de l'Institut Pasteur, 1900, xiv., 577.

Morgenroth. Münch. med. Wochenschrift, 1902, xlix., 1033.

Néfédieff. Ann. de l'Institut Pasteur, 1901, xv., 17.

Schütze. Deutsche med. Wochenschrift, 1900, xxvi., 431.

Weiss. Archiv f. Gesammte Physiol., 1896, lxv., 215.

DISCUSSION.

Dr. R. C. Cabot: I want to remind the members very briefly of the work done upon this subject two years ago by Dr. Franz Pfaff and Dr. Vejus-Tyrode and reported at the meeting of the American Physiological Society in 1901.

The authors approached the subject from quite a different point of view and as a part of their pharmacologic studies.

They made a number of experiments in the endeavor to secure the secretion of normal urine by the kidney outside the body. Defibrinated dog's blood prepared under aseptic conditions was made to circulate through the isolated kidney, and there resulted a secretion of urine, but not of normal urine. Blood, albumin, and casts of various sorts were found in the fluid secreted by the isolated kidney, together with a diminished quantity of urea and other solids.

Following up this subject, the authors bled a healthy dog, defibrinated the blood, and reinjected it into the dog. They found that this substance produced in the living animal a secretion of urine very similar to that previously obtained by causing defibrinated blood to circulate through the isolated kid-

ney. They showed by this experiment the powerful effects of defibrinated blood upon the normal kidney.

Later in their experiments, after having produced in a dog a nephritis of the type and by the means above described, the authors bled the animal until it was nearly exsanguinated, and then they transfused the whole blood of another without defibrinating it. As a result of this operation the albumin and casts disappeared, the amount of solids rose to normal, and the kidney resumed in all respects its normal functions.

The authors do not offer an explanation for these changes, but they may be explained, in that the defibrinated blood makes normal metabolism impossible, and on account of the lack of proper nourishment the cells in the kidney lose their normal function.

Dr. Flexner: I have followed this work with great interest, and it seems to me this is a very definite contribution on the subject of nephritis. As the doctor has said, the most important results came from the least suspected sources; that the blood serum of dogs with spontaneous nephritis was capable of setting up in the normal dog an acute nephritis, and that the blood of the second animal when introduced into the third was still capable of causing a similar condition. It illustrates that the degeneration of kidney tissue in the body is a matter of very great consequence.

Metchnikoff showed that animals could develop a substance that would produce the trouble in the second animal. The fact that this substance is still active in the third animal would indicate that it is not some accidental chemical substance circulating in the blood. That it is not a living agent seems proved by the failure of attempts to cultivate bacteria. The effects are not due to ordinary bacterial or chemical substances, but to the products of epithelial degeneration accumulating in the blood. These substances, if injurious to the second and third animal, may be injurious to the animal itself. Where these lesions go on through years and years, and in which the cause is very obscure, they may have had a beginning in acute infections. If these products can accumulate in such a manner and in such quantities as to injure other animals, why might they not be injurious to the cells of the animal itself?

Dr. Sewall: I understand that the injection of the serum of an animal with nephritis will start up in the sound animal the production of substances which injected into the blood of a third animal will cause a nephritis.

It would be a matter of exceeding interest to determine in what organ or tissue the production of substances giving rise to nephritis is carried on. One would think that if, in an animal suffering from induced nephritis, the blood were collected separately from various organs, it might be possible to determine by the injection of such portions of blood into different animals in which organ the nephritis-producing substance is formed. I should like to ask if this line of investigation has been pursued?

Dr. MacCallum: I should like to ask as to whether there was a quantitative increase in the toxin in the third animal? whether the same quantity of blood as in the second would produce the same symptoms?

Dr. Pearce: I used blood only from the terminal vein, and did not use it from the veins of the various organs. The normal serum produced no effect. In two instances the dogs had received injections of serum from the normal animal with no change.

As to the second question, the nephritis in the third dog was of a much milder grade than in the second. The condition in the first dog was that of a nephritis that had been going on for a long time. The condition in the second dog was less, and in the third dog much less marked. I have a dog now under observation that has received two injections of this serum. The condition of the urine cleared up after the first injection, but since the second injection it is as marked as before and has assumed a chronic condition.

ON THE VISCERAL MANIFESTATIONS OF THE ERYTHEMA GROUP OF SKIN DISEASES.

[THIRD PAPER.]

By WILLIAM OSLER, M.D.,
OF BALTIMORE.

According to the classification of recent writers under the erythemas—les erythèmes of the French—are included simple erythema, erythema exudativum, herpes iris, erythema nodosum, certain of the purpuras, urticaria, and angioneurotic edema. The essential process is a vascular change with exudate, blood, serum, alone or combined. While five or six of the affections just named are described usually as separate diseases they belong to one family, and are characterized by the similarity of the conditions under which they occur, the frequency with which the lesions are substituted the one for the other in the same patient at different times, the tendency to recurrence, often through a long period of years, and, lastly, the identity of the visceral manifestations. In the latter for some years past I have been particularly interested, and in 1895 I published a series of eleven cases,[1] and in 1900[2] a second series of seven cases. In this paper I shall give a third set of eleven cases, and shall consider the features presented by the entire group of twenty-nine cases.

Eight only of the patients were under ten years of age; thirteen were between the tenth and twentieth years. There were eleven females and eighteen males.

The seriousness of the condition is attested by the occurrence of seven deaths in my series—24.1 per cent.

[1] American Journal of the Medical Sciences.
[2] Jacobi Festschrift and British Journal of Dermatology, vol. xii.

Case XIX. *Onset, with erythema over cheeks and nose, in October*, 1889; *puffiness of one small joint; edema of one eyelid; increase in the erythema and swelling of the face; marked puffiness and stiffness of the hands; recurring attacks of erythema of the face and local infiltrations in different parts of the body; slight fever; in March very high fever, to* 105°; *much swelling and infiltration of the face and neck; acute nephritis; persistence of edema of face; death in uremia May* 13, 1900.—Miss C., Pittsburg, Pa., aged fifteen years; seen January 9, 1900. Father neurotic. No rheumatic history in the family. She has been a very healthy girl; is well grown. She began to menstruate at fourteen years. Large framed; has developed rapidly. Late in October, one Sunday returning from church, an erythematous blush of both cheeks was noticed, extending to the bridge of the nose. It was thought to be due to the sun, as it was a very hot day. As the congested condition of the face did not disappear, a dermatologist was consulted, who pronounced it eczema and gave her an application. For two weeks subsequently she showed a slight puffiness over the tendon of the left metacarpal bone of the middle finger. This disappeared quickly, then followed a puffiness of the left eyelid, and in a few days of the right eyelid, the erythema of the face changing in appearance, at times nearly fading. The eyelids were infiltrated and edematous (not red). The urine was repeatedly examined and was negative.

Just before Christmas the face became very much more swollen and the eyes were nearly closed. The erythema became much more intense. On Christmas day the backs of both hands over the middle metacarpal regions were very puffy and edematous (not reddened). There had been no itching or burning of the face or hands. She had one attack of pain under the left breast—pleurodynia, the physician thought—quite severe, relieved by three days' rest and local applications.

Present Condition. The patient looks remarkably well.

Face. There is a marked erythema, with swelling of both cheeks and the nose, and to a less extent over the chin. It had a purplish-red look as she came in from the cold air. After rest in a warm room it became of a brighter red. On the cheeks it extends to within about 1½ cm. of the angle of the mouth, a little more extensive on the left than on the right. The nasolabial fold, the whole of the under lip, and the greater part of the upper lip are uninvolved. The nose is involved, about the same color as the cheeks, and a slight extension can be seen over the supraorbital ridges, a swelling and a slight blush of redness. The eyelids are at present only a little puffy; the conjunctivæ are slightly congested; on the chin the patches are discrete; individual isolated spots, slightly infiltrated and a little raised, and extend under the chin and behind the ears. There is no ecchymosis. The tonsils and pharynx look natural.

The left hand feels stiff, and to make a fist is painful. On the back of this hand, during Christmas week, there was a large serous infiltration of a few hours' duration. There is now only a slight patch of erythema over the second metacarpal bone of the middle finger. On the back of the right

hand there are a few scattered patches. On the back of the fingers of the right hand there are raised reddened patches, the largest one on the index.

Dr. Duhring, of Philadelphia, saw the patient the next day, and regarded the rash as a peculiar form of erythema.

The subsequent history of the case is as follows:

On February 6th the doctor wrote: "The lobes of the ears have desquamated, leaving a normal appearance, except a little dry, thin scale, not yet loosened; the redness and puffiness of the lobes have disappeared. The upper outer angles of the redness of the cheeks show a tendency to desquamate; a little roughness of the skin; thin, scaly epidermis. The upper lip, which was blotchy, has desquamated, the base being still red. The contour of the face is improved; the general erythema of the cheeks varies. The edemas and infiltrations change from point to point: upper eyelids slight, one elbow from time to time, both knees or one knee, a finger or the back of the hand. On Sunday afternoon it developed beneath the tendo Achillis of left foot; previous to that both ankles on their outer aspects; last night the left ankle, the right knee, with some pain, and the right elbow was so stiff that it was difficult for her to use her knife or fork with that hand at dinner. Occasionally, when the edema is more prominent, there may be a feeling of heat to the touch, the temperature at bedtime ranging from 99.8° to 100°, to 100.2°, to 100.4°; at other times normal, morning and evening. The edema lasts from twenty-four to thirty-six hours, the back of the left hand week before last proving to be the most persistent. This morning in bed she had free movement of all her joints, showing that the disturbance of yesterday was passing away. As a rule, toward each evening she feels stiff, it may be in the extremities or hands, but by morning, unless the edema is prominent, the stiffness is not noticeable. The spaces beneath the quadriceps tendon, the tendo Achillis, and beneath the malleoli of the ankles, and the metacarpals are the points now where the swellings occur. The eyelids have never been so bad as during Christmas holidays. Locally the face looks badly enough. Physically, notwithstanding the recurring edema, I consider her better than one month ago. In animation and general good spirits she is becoming more natural, though the going out among people requires some pluck and determination."

On February 19th I saw the patient in Pittsburg. She seemed somewhat better, but she had still the swelling of the face and of the ear, and occasionally erythematous patches over the nose. For a few days she had had a little fever, up to 100°, and the day I saw her she was not feeling so well and the temperature had risen to 103°. The spleen was palpable. Then for a month she had a very severe attack of extensive inflammation of the skin of the face. She had high, irregular fever, ranging to 105°, and the doctor writes: "The force of the trouble, whatever the cause, expended its power on the face and neck. No clinical picture could compare with it in my experience, except that seen in erysipelas—I mean in dimension, appearance, and parts involved. The extremities have remained perfectly free.

The submaxillary and sublingual glands—in fact, the entire circumference of the neck was distended. The infiltration was so extensive that on March 2d she complained of pain in the left ear, and on March 5th the right ear was in the same condition, marked dulness of hearing, and on March 14th paracentesis of the drum had to be performed. The drainage relieved her." The temperature did not begin to fall until after March 20th.

On April 10th the doctor wrote: "Her condition is no worse than when you last heard. The pathologic process, whatever it is, is confined to the face and forehead. The rise and fall in the morning and evening temperature keeps about the same, varying from 99.8° to 100°. The glands of the neck are not so large. There is some edema of the parts. For several days in the late afternoon she is having a pretty severe frontal headache, which prostrates her. Her appetite is good, and she sleeps well. She sits up a little every day, but soon tires. She is taking a dessertspoonful of Basham's mixture with a sixtieth of strychnin. I have been hoping that no more serious complications might arise, but it is evident that we are not at the real cause of the trouble. The report of the urine is as follows: Specific gravity, 1016; considerable amount of albumin, a few red blood corpuscles, hyaline and waxy casts.

"Since you saw her there has been but one outbreak of the edema such as appeared at the beginning; it came on the back part of the left hand last week, and persisted for twenty-four hours."

On May 17th the doctor wrote: "During the latter part of March and the first part of April she was gaining. On Easter evening there was a rise of temperature, the albumin increased rapidly, and nausea and vomiting became very distressing. She had perforation of the drum of the right ear. The edema of the face persisted. During the last week of life the left eye was closed entirely and the left half of the face was tense with edema. The amount of urine diminished to two and a half ounces in the twenty-four hours. The mind kept clear. She died of uremia on Sunday, May 13th, 1900."

This case and No. XXVI., which presented many points of similarity, illustrate the very grave character of some of these obscure forms of erythema. Here was a healthy young girl of good family history who had a persistent erythema of the face and hands, with areas of angioneurotic edema; then three months later a more severe attack, with fever and intense swelling of the face and an acute nephritis, which proved fatal seven months after the first appearance of the erythema.

Case XX. *Attack of severe colic; admission to the surgical side for suspected appendicitis; a week before a purpuric eruption on the legs, with high-colored urine; rash of exudative erythema on the legs, with here and there purpura; no involvement of the joints; acute nephritis, abundant albumin, and*

blood casts, and a small amount of blood in the stools; recovery.—This case is particularly interesting on account of the fact that he was admitted to the surgical side of the hospital with abdominal symptoms, which were suspected to be due to appendicitis.

Milton R., aged fifteen years, admitted March 14, 1900. He had been a healthy boy; never had rheumatism; no rheumatism in his family. He had never had similar attacks, though his mother said he had irregular, colicky pains at times, and once of such severity that he vomited with it.

Present Illness. About March 7th he noticed himself that the urine was very dark. He had had, a week or so before, some colicky pains in the abdomen.

With the highly colored urine there was no pain in the back, micturition was not painful, and there was no increased frequency. About the same time it was noticed that his legs were somewhat swollen and peppered with red spots, which continued to come out at intervals. The boy had been going to school and had seemed quite well up to this attack.

On admission he was a well-nourished, healthy-looking boy. There was no rash upon the face. Symmetrically arranged on the arms and elbows and about the wrists and hands were a few patches of a rash, chiefly discrete, consisting of papules 1 mm. to 3 mm. in diameter, some distinctly raised, many of them capped with small vesicles, which in places were drying. About the elbows the patches were larger, more raised, and had a purplish-red color. They varied in size from a pin's head to 5 cm. in diameter. In the larger areas the centers were more yellowish in color, the periphery purplish-red. The color did not entirely disappear on pressure.

On the legs there was an extensive symmetrical rash about the ankles and knees, the patches very diffuse, on the legs more discrete. On the outer sides of the legs there were patches 3 cm. by 1.5 cm., slightly raised, and these presented three grades of color, the center whitish, a reddish-brown staining, and then a zone of brighter red. Scattered between the larger areas were some distinct purpuric spots.

Heart. Apex-beat in fifth, 7 cm. from midsternal line, rather diffuse, no thrill, soft apex systolic murmur heard over the body of the heart.

The abdomen looked natural, soft to touch; liver not enlarged; spleen slightly enlarged, the edge distinctly palpable below costal margin. Slight general enlargement of lymphatic glands; reflexes normal.

The urine on admission was blood-red, specific gravity 1014; contained many granular casts, large and small, and some red blood casts; abundant albumin. I remarked to the class the first day how interesting it was to see a case of acute hemorrhagic nephritis without any diminution in the amount of urine, with no swelling of the face and no trace of edema. The temperature was 100.5°.

Blood. Hemoglobin, 60 per cent.; red blood corpuscles, 4,156,000; leukocytes, 6800; coagulation time, two minutes and a quarter. On March 3d blood cultures were taken, which were negative.

The rash gradually faded and no fresh spots of exudative erythema appeared, but on several days between the 18th of March and the 1st of April small purpuric spots appeared; some minute ones on the palms of the hands.

On March 18th the patient had a small stool containing clear mucus and bright red blood.

The boy progressed very favorably. The urine on the 17th was 1720 c.c. The bright red color persisted, and began to clear about March 22d. It remained smoky and had blood in it up to the middle of May. The albumin gradually disappeared. Red blood corpuscles, hyaline and granular casts were seen all through April.

On May 11th the condition was as follows: Smoky, 1013; acid reaction, trace of albumin, granular casts, red blood corpuscles, red blood-celled casts. The patient was reported as quite well in the autumn.

Case XXI. *Otitis; swelling of the hands and legs; extensive purpuric rash, in places papular; acute nephritis, with albumin, tube casts, and blood; cramps in the abdomen and vomiting; recovery; subsequent admission with meningitis from the otitis media; death.*—John D., aged twelve years; seen April 24, 1900. He complained of running from the left ear and swelling of the hands. His family history was good; no similar troubles that he knows of; no rheumatism. Except summer complaint when he was two years old, he has been an exceptionally strong, healthy boy; has had no acute infectious diseases. About two weeks before he applied at the Dispensary he had a running from the left ear. Five days before application his hands and legs became very much swollen, and he could not put on his shoes. The day before application a rash came out on the legs.

Present Condition. Fairly well-nourished boy, but he looked anemic. The face and eyelids were somewhat puffy. Evidence of recent epistaxis about the nostrils. The hands looked swollen and edematous. The pulse was rapid, regular. There was no enlargement of the heart. The first sound was rather thudding, and the second pulmonic was accentuated. Temperature, 101°. The abdomen looked full; the spleen was easily palpable. The liver was not enlarged.

Below the knees the legs were much swollen, firm, and did not pit on pressure. There was an extensive petechial rash, papular in places, but nowhere with much swelling. The urine showed albumin and coarsely granular tube casts; no red blood corpuscles. He was ordered an iron mixture.

April 27th. The patient came again to-day; says he feels very much better. The edema of the legs has almost gone and the rash has faded. The urine shows abundant albumin, numerous coarsely and finely granular and hyaline casts.

May 1st. Since the previous note the patient has had recurring attacks of severe cramps in the abdomen, with vomiting. The mother describes the material brought up as at first bloody, then black, and later yellow. The swelling of the face and feet is almost gone.

4*th*. Patient has vomited every evening since the last note; has not vomited to-day; does not complain of any pain.

10*th*. Patient began to vomit on waking, and continued to do so at intervals during the morning.

12*th*. He has had no nausea or vomiting since the last note. The legs are not edematous. A few stains of the purpura remain.

14*th*. The urine is light-colored, cloudy, 1 per cent. of albumin by Esbach, and contains a large number of red blood corpuscles, finely granular casts, and casts of red blood cells.

On July 30th the boy was admitted to the hospital with acute meningitis from the otitis media. He was removed by his parents on August 1st, and he died a few days later.

CASE XXII. *Swelling of the legs, with purpura and pains in the knees and ankles; colic; acute nephritis, with blood, albumin, and tube casts in the urine; recurring attacks of purpura with urticarial wheals; recovery.*—Edna C., aged six years; seen May 11, 1900, with Dr. Richardson, of Bel Air. Family history good. The child had been well and strong; never had rheumatism or chorea. Five weeks ago, about 4 P.M., the child complained of pains in the legs, and the mother noticed that they were swollen, and dark blotches came out. The legs became swollen as far as the knees, and it was difficult for her to move the knees and ankles. She has had for a year or so slight colicky pains in the stomach. On the following day Dr. Richardson found a good deal of albumin in the urine. On the day of the attack the urine contained blood. She has got pale, has had several recurrences of the blotches on the legs, and has with it much colic. Yesterday she had a very severe attack.

She is a fairly well-grown child; looks a little pale and brown, partly sunburn. Color of the lips pretty good. No swelling of the eyelids; no puffiness of the wrists. The tongue is clean; no swelling of the joints. There is a fresh crop of blotches, which came the night before last. The original crop was more than this. At present there are large areas 2 cm. across, slightly raised, evidently fading spots of urticaria, with purpura. Then there are in addition spots of simple purpura scattered between these large areas. The purpura extends as far as the hips. The spleen is not palpable, liver not enlarged. The apex-beat is within the nipple line, no thrill; heart sounds are clear. The urine has been albuminous at times.

The urine to-day had a specific gravity of 1024, clear, acid reaction; contained neither albumin, sugar, casts, nor red blood corpuscles.

March 13, 1903, the mother writes that there has been no recurrence of the purpura.

CASE XXIII. *History of attacks of pain in the knees; colicky pains, with nausea and vomiting and diarrhea for many years, sometimes with swelling of the feet; enlargement of the spleen; recurring attacks of purpura, with abdominal pain and vomiting; outbreaks of erythema; recovery.*—Sarah E. W., aged fourteen years, admitted September 10, 1900 (Med. No. 11859), complaining

of stomach trouble. Her mother had had rheumatism. She herself has an indefinite history of rheumatism, irregular pains, and has had three or four attacks in which her knees have been painful; no swelling, no redness, no fever. She had been subject to sore throat, especially three years ago. At times she has had attacks of vomiting. The child's mother states that she was well and natural until the attack of measles at her fourth month. Ever since she has had two serious troubles: first, attacks of abdominal pain, with nausea, vomiting, and diarrhea; and, secondly, skin rashes, which come out suddenly and then fade away. They are usually symmetric. With these attacks there is often swelling of the feet, which comes very rapidly.

For three weeks she has been having pains in the abdomen, and for five days past there has been much nausea and vomiting; three days ago she had diarrhea—five or six stools a day. She felt feverish, had some sweats at night, and loss of appetite. She has had to get up at night once or twice to pass urine. Eight days ago the feet and legs began to swell, and a red rash broke out on the skin. The knees were painful, and her eyes at the same time became puffy. The swelling of the legs has disappeared and she has been a good deal better.

On admission she was a small, pale, frail-looking child, not anemic, eyelids slightly puffy. The temperature was 100°; pulse 116, slightly irregular. There was a somewhat diffuse heart-beat in third, fourth, and fifth; on palpation a systolic thrill; on auscultation a blowing systolic bruit transmitted to the axilla; accentuation of the pulmonic second. The abdomen looked natural; the liver was not enlarged; the spleen was fully 2 cm. below the costal margin. There was slight edema of the feet and ankles, and there was a fading rash on the knees, elbows, over the clavicles and ankles. Some of these spots were distinctly purpuric. One above the left external malleolus was a bluish spot, looking like a bruise.

September 13*th*. Had an attack, with great coldness of the feet and a burning sensation in the pit of the stomach, which increased so that at 10 P.M. she had a great deal of abdominal distress. A fresh, brilliant red rash in raised patches came out on both buttocks, extending down the thighs, and on both elbows. The abdominal pain persisted that night, and at 6 A.M. she vomited, at first curds, later a greenish fluid, and about 9 o'clock mucus mixed with blood.

14*th*. There is this morning an abundant purpuric rash over both buttocks, extending down the thighs, up the back on each side, over the elbows, and the upper arms. The rash is raised, and the individual spots have distinct margins. On the right elbow there is a bluish-red discoloration, which is painful to the touch. There is no pain or swelling in the joint itself. She had to have morphin. Throughout the day she vomited several times.

Blood. Red blood corpuscles, 3,680,000; leukocytes, 10,000; hemoglobin, 75 per cent.; blood coagulation time, four minutes.

Urine. Specific gravity, 1012; no albumin, no blood, no tube casts.

15*th*. The rash is very extensive over the back. Some of the purpuric

areas are infiltrated and raised and measure 5 x 3 cm. There is a little swelling in the left elbow-joint to-day. There are red blotches on the thumbs and over the knuckles. The spot where the hypodermic needle was inserted is surrounded by a hemorrhage.

16*th*. The swelling of the left elbow has disappeared. There is a fresh erythema on both forearms. From this time the patient improved. There was a good deal of pigmentation and staining left by the hemorrhages. She was discharged, feeling quite well, on September 24th.

Case XXIV. *Erythema and purpura; acute nephritis; general edema; persistence of the albumin for two months; gradual recovery.*—Morris S., aged three years, Hebrew; admitted December 20, 1900, with swelling of the face, abdomen, penis, and legs. There was nothing of any moment in his family history; no rheumatism. He was healthy as a baby; had a sore navel for some time. When two years old he had diphtheria, a severe attack, not followed by any swelling of the feet. With this exception the child has been very well. He has grown and thriven, eats heartily, and drinks three large cups of coffee in the day! Three days ago the father noticed some red spots on the back of the left hand, which looked like bites of insects. At the same time there was swelling of the wrists and back of the neck. That night the swelling became worse and the spots extended and formed large blotches. The father said the wrists looked as if they had been scalded. On the following day the spots appeared on the legs and body and became darker. The penis became edematous.

I saw the child at my out-patient clinic and made the following note: There is well-marked purpura over the legs and around the crests of the ilia, and there is a general subcutaneous edema of a brawny character. The skin of the penis is edematous. The swelling and edema which had been so marked on the wrists has disappeared and has left a brownish-red stain. The abdomen is large; there is dulness in the flanks; no percussion wave. Some edema of the lower part of the back. On the outer surface of the skin of the right arm there are stains of a purpuric rash. Examination of the urine showed a large amount of albumin, but no tube casts.

The child was taken home by its father the same afternoon, but returned three days later with general anasarca and signs of slight fluid in the abdomen. The child looked very well. The face was only slightly swollen, the eyelids a little puffy. The urine had a specific gravity of 1023, dark yellow in color, and there were a few casts and much albumin. Throughout the month the dropsy persisted to a slight extent, but gradually disappeared. A very careful daily study of the urine was made, particularly with reference to the percentage of albumin and urea. The amount of albumin varied through January from 0.1 to 0.3 per cent. On the 17th, 18th, and 19th of February the amount increased rapidly, reaching on the 20th 1 per cent. There were no tube casts. On March 5th, for the first time, the urine was free from albumin. Then again, from the 25th to the 30th, the albumin returned, and reached on the 28th 0.5 per cent. From that time on the

albumin was absent, and he was discharged April 21st in good condition. I heard on March 1, 1902, that the patient has remained perfectly well.

Case XXV. *For the first six years of life recurring attacks like nettle-rash; then to the tenth year freedom; in tenth and eleventh years recurrence of the rash in larger blotches and much swelling of the face and eyes; recurring attacks of severe spasmodic croup, having no special relation to the skin rash; twice with these attacks there has been swelling of the throat; lately marked swelling of the soft palate and uvula; swelling of the feet and of the face; no nephritis.*—N. D. D., aged fourteen years, Lafayette, Ala.; sent May 6, 1901, by Dr. Love. When three weeks old red splotches came out all over him and itched like nettle-rash; lasted three weeks. It recurred periodically until he was six years old. He never passed six months without an attack; sometimes they would occur quite frequently. He had no pain in the abdomen with the attacks, no vomiting. From the age of six to ten years he was perfectly free from the attacks. At ten years the trouble reappeared, and recurred periodically until he was eleven years old. Good health until the thirteenth year, when the disease returned. The "splotches" were larger and there was swelling of the eyelids and face. About six weeks ago the inside of the throat began to swell, chiefly the uvula and the soft palate, and there was edema of the outside of the neck. He has had one attack also in the left auditory canal. The last attack was ten days ago. The feet began to swell and he could scarcely get his boots on. The face was a little swollen in this attack.

The family history is good. The father has a quinin idiosyncrasy, and cannot take even a few grains without having a skin rash. An uncle also has the same peculiarity.

He is a healthy-looking boy, of good color. No swelling of the face to-day. The remnant of an urticarial spot just above the right eyebrow. The only eruption at present is above the popliteal space on the left side, where there is a large spot extending across the lower third of the thigh, measuring 8 x 10 cm. It is reddened, prominent, greatly infiltrated, the margins localized and distinct; a dusky red color, in places of a more vivid red; very hot. In one or two places the margins look a little less red. The hyperemia is extreme, and pressure fills up at once. There is nothing at present in his throat; no other spots anywhere.

The heart sounds are clear; arteries not sclerotic. Pulse is good. Hemoglobin, 80 per cent. Urine: no albumin, blood, or tube casts.

All through his life he has been subject in the winter to attacks of severe spasmodic croup, which have not apparently had any relation to the skin rash. It has recurred at intervals all his life, twice with marked swelling of the throat. It commences with difficulty in breathing, and lasts twenty or thirty minutes. He will call and say he is about to choke. Wet cloths about the throat relieve it. No cough with it.

May 8th. The swelling in the patch of the day before yesterday has subsided. There is left a bluish-green stain like a bruise.

I heard from Dr. Love on February 23, 1903. The boy is very much better. He has had no attack for two months. He took calcium chloride for a long time with benefit; recently camphor in three-grain doses four times a day, which seems to have had a very satisfactory influence.

CASE XXVI. *Onset in September*, 1901, *with erythema of the nose and cheeks; extension to the elbows and arms, usually in the form of wheals, but some spots purpuric; chill, followed by consolidation of the lower lobe of left lung; protracted fever; enlargement of the lymphatic glands; delayed resolution of the pneumonia; urine clear in the attack; gradual recovery; in May*, 1902, *onset of acute nephritis; uremia: death in a convulsion.*—L. E., aged twenty-four years; seen at Pittsburg, Pa., on February 6, 1902, with Dr. Litchfield. Her family history was good; no rheumatism; no tuberculosis. She had been a very robust girl; no serious illnesses. Toward the end of the summer, when at the Thousand Islands, a rash began on the face, chiefly on the nose and cheeks. It looked, the doctor said, like lupus erythematosus. It persisted, and troubled her a great deal. Dr. Fox, of New York, who only saw her once, writes that he thought it looked like an acute lupus erythematosus. It spread in patches to the body, particularly about the elbows and on the arms. The patches were red, sometimes raised, and would, at times, come out like wheals. Before Christmas she had a very violent outbreak, and many of the spots became purpuric, and on the arm the doctor said there were spots which looked almost like the eruption of vaccinia. On December 27th she had a chill, and on the third day consolidation of the left lower lobe was found. The temperature was 104°. From the fifth and sixth days there was a drop in the temperature. On the twelfth day it dropped to 98°; then it gradually rose, and from the twelfth to the twenty-sixth day it ranged to 105°. Then the other lung became involved. There was very little cough, particularly after antipneumococcic serum was given. There were no true chills. The mind was clear, as a rule. For the past three weeks the temperature has ranged about 101°, with no very great drops. The pulse has been from 112 to 120; respirations 22 to 40; mind clear; no delirium. The right lung has been clearing. The left lower lobe has been solid for some weeks. About two weeks ago the left leg became swollen, and she had a thrombus in the femoral vein. For ten days the lymphatic glands throughout the body have been a little enlarged and tender.

At the time of my visit the patient looked thin and pale. There was no sign of any rash on the face, but there was erythema of the skin of the thighs, mottled and patchy, and in places a little raised. There was no purpura. The left leg was swollen, but was no longer tender. She had complete consolidation of the lower lobe of the left lung, with tubular breathing and a few râles. The fremitus was not very marked. I put in a needle in two places, but got nothing. The Widal reaction was negative. The sputum was a little rusty, and I had some examined. There were pneumococci, but no tubercle bacilli.

The urine was examined repeatedly, and there was occasionally a faint trace of albumin, but nothing special. She was anemic, and on January 29th

blood count showed: red blood corpuscles, 3,310,000; hemoglobin, 46 per cent.; leukocytes, 6000. The patient gradually improved through March and April, and seemed to be getting quite well. In May she went to Atlantic City, where she improved rapidly. Toward the end of the month an acute nephritis came on, without any special exposure; the urine was scanty, high-colored, contained blood and tube casts and much albumin. There was fever, 101° to 102°; no skin rash. I saw her with Dr. Marvel shortly after she had had a uremic convulsion. She died within a week of the onset of the nephritis.

Case XXVII. *From infancy recurring attacks of colic, sometimes with vomiting; recurring attacks of blotches (erythema) on the skin of face and arms; at the time of examination a spot of erythema capped with blister.*—Dorothy B., aged thirteen years, referred to me by Dr. Charlton, of Savannah, Ga., June 18, 1902, for a peculiar trouble in her stomach. She was healthy when born, was a healthy child, and has grown and developed well. The family history is good; no special peculiarities. Since infancy she has had a peculiar stomach trouble, recurring attacks of nausea, and colic-like pain. The attacks recur at irregular intervals, a week or two apart, sometimes a number in succession, and then she will be free for several weeks. She will appear perfectly well, will eat a good meal, and an hour or so afterward will say, "May I go and lie down? I have a pain in my stomach." The attacks are chiefly in the morning. The abdomen seems tender and the colic at times has been severe enough to make her cry out. It has been a source of constant worry, and nothing has ever seemed to do her any good. At times she has had very obstinate vomiting with the attacks. Her mother says the pain is always in the pit of the stomach. When four or five years of age she had a very bad attack of "ivy-poisoning." This spring some red spots came out on the neck, and she has had them recurring ever since. They occur on the face and arms as red blotches, and then become capped with little blisters.

The patient is a healthy-looking girl; color good; tongue clean. The abdomen is soft, natural looking; spleen not enlarged; stomach not dilated; no enlargement of the liver. No sensitiveness anywhere on pressure. The heart is not enlarged: the first and second sounds are loud. There is a soft systolic murmur at the base. The skin seems everywhere clear, except on the left foot, just above the middle toe. Here there is a raised, infiltrated, reddened spot about 5 x 5 mm., capped with a small, clear blister. This, her mother says, is the typical appearance of the rash. When the attacks are bad a number of these appear on the face and neck, and they come out on the extremities, looking at first like hives, and then are capped by the little blisters. The urine is clear; no blood.

A letter from her mother, March 22, 1903, states that the child has improved very greatly, and has been very free from that colic, and has had no return of the skin trouble.

Case XXVIII. *For two years recurring attacks of purpura, chiefly on the legs; severe attack three months before admission, with colicky pains, vomiting,*

diarrhea, and arthritis; in the last attack diarrhea was a marked feature, with the passage of blood from the bowel.—A. S. A., aged twenty-six years, white, single, lawyer, Montgomery, W. Va.; admitted February 12, 1902, complaining of skin disease and stomach trouble. No similar trouble in family; no purpura. Patient's father has chronic diarrhea. Usual diseases of childhood. Typhoid fever in 1898, slight attack, but followed by a gastric (enteric?) trouble lasting about four months. Patient was in bed altogether about six months. He has had occasionally swollen and tender joints. One attack of swelling and pain about tendo Achillis. Appetite and digestion good prior to present illness. Tendency to constipation. Denies lues and gonorrhea. Habits good. Average weight, 160 pounds; present weight, 140 pounds. Patient first noticed the purpuric eruption on his legs in the spring of 1901, two years ago. At this time the spots were very small and situated only below the knees, especially about the ankles. At this time the patient had no nausea, vomiting, or diarrhea; no arthritis. During the summer of 1901 the patient had indigestion and constant recurrences of purpura; no arthritis; some nausea, vomiting, and pain. At no time was he confined to his bed or compelled to give up his work.

In December, 1901, the patient had his first severe attack, which kept him in bed for about a week, and was soon followed by another of about the same severity and duration.

For eleven months, until November, 1902, the patient was well; then he had very severe abdominal pain, with diarrhea, nausea, and vomiting, followed by arthritis and a hemorrhagic eruption on his legs. He was forced to give up work and go to bed, and until New Year's there were recurring attacks. During the last month or six weeks he has been at work, but has been feeling badly, with arthritis and purpura, some "indigestion," and pain.

The attacks are all of the same character. The patient first noticed the purpura on his legs or arms (at first it was only on his legs below knees, but is now on thighs above the knees, and on hands and arms, particularly on extensor surfaces), accompanied with a mild arthritis. The joints are "sore and stiff," but he can use them. This is followed by a severe pain in his left side and left half of abdomen, passing over middle line in a narrow band. The pain is fixed, not radiating, and of a cramp-like character; sometimes requiring morphin by the mouth or hypodermically for relief. The pain usually lasts about two days. Following the pain the patient has diarrhea and usually nausea and vomiting. The vomiting is the last event in the series, and about the time it begins the purpura fades, leaving brownish-yellow stains.

The joints attacked are usually the ankles and knees. In the last outbreak the left hand (metacarpophalangeal joints) was involved, and his wrists, never his elbows, shoulders, or hips. Last November the patient passed considerable blood per rectum of a very dark color. He has never had hematemesis or hemoptysis. Slight epistaxis. No hematuria or bleeding from gums or mucous membranes. He has grown quite pale in each attack, and loses flesh rapidly, but regains it quickly.

Present Condition. Well nourished, but pale. Examination of heart, lungs, and abdomen negative. There is a purpuric eruption on back of hands and arms, more on right arm than on left, and on extensor than on flexor surfaces; same on feet and legs up to the groins. Tenderness and subjective feeling of stiffness in left hand (metacarpophalangeal joints) and right wrist. Blood pressure, 145 mm. of Hg. Red blood corpuscles, 4,280,000; leukocytes, 7600; hemoglobin, 65 per cent. (von Fl.). Blood coagulation time, six and a half minutes. Urine negative.

On February 13, 1902, I made the following note: Patient is pale, sweating profusely. Tongue furred. Skin of face clear. Gums not swollen; a little red line; no blue line. There is a fading purpura on the arms; spots not raised, brownish, leaving stains, chiefly on flexor surfaces. No purpura on trunk and back. On the legs there are numerous stains of fading purpura over feet and extensor surfaces. The spots are larger on the legs. All are now fading. Joints nowhere red or swollen.

Circulatory System. Slight sclerosis of arteries. Apex-beat visible in fourth left interspace, just inside nipple. Soft murmur at apex with first sound and over body of heart, not propagated to axilla.

Abdomen looks natural; nowhere painful; a little tender in spots over colon. Spleen not enlarged. Liver not enlarged. Appendix not palpable. Superficial glands not enlarged. He was ordered calcium chloride.

February 14th. Blood coagulation time, six and a half minutes.

16th. Purpura has almost disappeared. Patient has improved very rapidly. On his discharge a few days later the patient looked very well; blood coagulation time was three minutes.

Case XXIX. *Acute otitis; arthritis; recurring attacks of colic with occasional vomiting; hemorrhage from the bowels; purpura; acute nephritis; recovery.* —March 7, 1903, E. F., aged five years, seen with Dr. Hamburger, to whom I am indebted for the notes.

Personal history. He had a prolonged attack of summer diarrhea two years ago. It followed an attack of otitis. For the past two weeks he has had pain in the ears. Last Wednesday (to-day being Saturday) there was a discharge from both ears. Fever has persisted off and on since the onset. This morning he was unable to stand on his feet because of pain. Temperature, 100.5°. There is a purulent discharge from the right ear. Heart sounds are clear. Examination of the lungs negative. The spleen is not palpable. There is no tenderness in the abdomen. The dorsum of the right foot is swollen, not reddened, but very tender on palpation. There is some tenderness, but no swelling over the left foot.

March 8th. The patient had a restless night. His temperature rose to 102°; this morning it is 99.7°; pulse, 104. He has complained of pain in the wrists and in the interval between the thumbs and first fingers. He has pain in the abdomen, accompanied by vomiting of the milk. Heart sounds are clear.

9th. The patient was unable to retain food yesterday, and he has vomited this morning the nourishment, as well as some bile independent of taking

food. Throughout the night he has cried because of intermittent pain in the abdomen, referred now to the left half and to the umbilical region. His temperature this morning is 99.6°. The tongue is heavily coated. There is a decided fetor auris. Every few moments he cries out with pain in the abdomen, which lasts a few minutes, then disappears, only to return in from ten to twenty minutes. He rolls over in the dorsal decubitus in these paroxysms. The joints are no longer sensitive. The abdomen looks natural. The left half is sensitive on palpation, particularly in the iliac region, while above in the upper half a fine gurgling can be detected. The abdomen is exquisitely tender during the painful period. Following an enema, a quantity of blood, sufficient to discolor the water a deep, dark red, was ejected with some fecal material. Early this morning he had a small movement (a couple of scybalæ) without blood. For the past four or five days the ears have been irrigated with 1.44 of bichlorid of mercury to one quart of water three times a day.

10*th*. The boy had considerable pain during the night. Yesterday afternoon about 3.30 he passed about one ounce of pure blood. This morning he is comfortable. Pulse, 120; temperature, 98°. The tongue is coated, but it is clearing at the tip and sides. There is no gurgling over the abdomen. There are no petechiæ. He is being fed on albumin-water, and toward evening is given a starch and laudanum enema.

11*th*. The pain returned about noon yesterday. It was so intense that at 5.30 P.M. the starch and laudanum enemas were resumed. He had two stools, composed mainly of blood and in part of the enema. The night was restlessly spent in pain. Early in the morning he passed a bloody stool. The temperature this morning was 97.8°; pulse, 108. To-night the temperature is 98.6°; pulse, 93. The day was relatively comfortable and free from pain, but this afternoon about 6.30 the colic returned with such intensity that the patient cries out. There is no skin eruption. The starch and laudanum enemas are being discontinued and he is being given paregoric, half-ounce, every two hours.

12*th*. The colic continues this morning. He has had two stools to-day, one being composed of narrow, long casts, dark brown in color, evidently composed of changed blood. The other stool contains curded milk, blood, a little mucus and some fecal matter.

Urine acid, 1026, yellow, no albumin, no sugar.

13*th*. He had a great deal of pain during the night. This morning at ten he was given one-half ounce of castor oil. At 3.20 P.M. he had a stool approaching the normal. To-night another movement of blood and fecal matter. The day was quite comfortable, but beginning at about 8.30 the colic returned. Paregoric, twenty drops, and deodorized tincture of opium every two hours.

14*th*. The boy was very restless until 3 A.M.; from that time on he has been comfortable. He had a normal movement this morning and another this afternoon without blood. This afternoon he had very slight pain.

19*th*. Last night a slight eruption was noted. To-day, scattered over the

legs, feet, and buttocks, are fine petechiæ, and on the calf of the left leg there is a bluish ecchymosis about 2.5 x 1 cm. in diameter. On both elbows there is an eruption formed by the coalescence of rose-colored, slightly raised papules. He has lost his appetite. The tongue is again lightly coated.

20th. The little fellow had an uncomfortable night, being restless and complaining of pain in the abdomen. This morning his appetite is poor. Temperature, 98.8°. The petechiæ persist, and in addition he has a subcuticular steel-blue ecchymosis over the right hypothenar region. It is here that he complains of pain. The eruption on the right elbow has almost disappeared, leaving little brownish discoloration. On the left it still persists, although less evident. On pressure it is not entirely effaced, still leaving a brownish color. The urine is yellow and looks a little smoky; acid, 1009; moderate flocculent sediment, containing a few hyaline casts and red blood corpuscles; albumin is present. His diet is now again limited to soft food. Castor oil is administered, and calcium chloride, ten grains, three times a day, is being given.

24th. The boy is again comfortable. He is very hungry; he looks pale. The eruption has disappeared, with the exception of a bluish discoloration on the calf of the left leg, representing the old ecchymosis. The colicky pain during the foregoing illness occurred in paroxysms at intervals varying from five minutes to an hour, On the 12th the pain was almost continuous. Between the attacks the little fellow would fall asleep, only to be awakened by pain, which caused him to roll about in great discomfort. So severe was it that he would cry out. The left lateral decubitus and lying on his face were the favorite positions during the painful periods. The abdomen was exquisitely tender during the colic. Throughout the illness the abdomen was slightly distended. The spleen was not palpable. The constant feature was a fine gurgling detected by palpation of the left half of the abdomen, particularly in its upper quadrant. The days were relatively comfortable, with the exception of the 12th, when the pain was almost continuous. The colic appeared toward evening, increased in severity through the night, reaching its maximum between midnight and three o'clock; then a decrease in its intensity and a more comfortable morning.

April 7th. A specimen of the urine sent from Atlantic City, where the patient went March 28th, is pale yellow, with a moderate flocculent, grayish sediment, containing many red corpuscles, some round granular cells, and an occasional hyalogranular cast, 1008; albumin present, 0.5 per cent.

11th. The patient returned from Atlantic City having gained weight and looking very well. Although the complexion is good, the conjunctivæ look a little pale. While in Atlantic City he once suffered from a little pain in his abdomen, and his mother noticed a few "spots" on his legs. The urine of to-night is pale yellow, acid, 1008; small flocculent sediment, containing many red blood corpuscles, a few hyaline casts. Albumin is present.

15th. The patient has been in bed and on strict milk diet, in spite of his dislike for this food. To-day he was much nauseated and vomited directly after taking.

16*th*. The urine is brown and smoky and deposits a reddish-brown sediment containing blood, some round granular cells and granular casts, 1024; contains much albumin. Very little fluid has been taken during the last twenty-four hours.

From the time he improved the albumin lessened. There were very few tube casts, and at the date of the last report, May 10th, he was doing well, though still kept in bed and on a milk diet as precautionary measures.

A criticism has been made on my previous papers that I had jumbled together a motley group of cases, some of purpura, some of angioneurotic edema, others of peliosis rheumatica; others, again, of exudative erythema. I did so on purpose, for I was seeking similarities, not diversities, and I refrained as much as possible from the use of specific terms, often, indeed, not knowing what to call a case watched for a long period. What, for instance, shall we call Case II., which I studied at intervals for six years—purpura, erythema, angioneurotic edema, or urticaria? The lesions varied from time to time, but there could be no question that all of them, with the extraordinary visceral symptoms, were manifestations of one and the same cause. Or Case XXVI., beginning with simple erythema, then crops of urticaria, and an exudative erythema with purpura and vesiculation? In Cases XIX. and XXVI. the most expert dermatologists were in doubt as to the nature of the lesions, and could only say that it was a peculiar type of erythema. On the other hand, the members of the erythema group have not all the same etiology, and, indeed, as is well known, the individual members have a very diverse etiology. For example, the urticaria of cholelithiasis, of an ague paroxysm, that caused by eating shellfish or strawberries, the urticaria of hydatids, and an asthma attack has the same clinical and anatomic features, though caused by a variety of poisons—bacterial, protozoal, vegetable, and metabolic. It is not unlikely that the poison in itself, of whatever kind, is of less intrinsic importance than certain transient aspects of cell metabolism. In the first place, there is no constancy of action of the same poison in different persons, or even in the same person at different times. This is notoriously the case with the animal and vegetable substances causing urticaria. In the second place, the chronic forms of urticaria probably illustrate a morbid and persistent sensitiveness of the cutaneous vessels to poisons of either intestinal or tissue origin. And, thirdly, the importance of the local

status is shown in that remarkable form of urticaria which comes on after exposure to cold. So long as the face is at a temperature above 60° the patient is all right; exposure at 40° is followed at once by an outbreak of urticaria. And, lastly, a peculiarity that may be transmitted through several generations, as in angioneurotic edema, which is only urticaria "writ large," must either be a morbid susceptibility of tissue or an inherited peculiarity of metabolism, or both combined.

The relation of the erythemas to infective processes is interesting. Certain types of exudative erythema behave like an acute febrile disease, and Dühring, of Constantinople, has described an epidemic form. In many of the fevers—typhoid, pneumonia, rheumatic fever, etc.—there may be symptomatic erythemas. The severer forms of purpura urticans with arthritis and colic (Henoch's purpura and the peliosis rheumatica) may run an acute febrile course with heart complications. Many of the graver cases of purpura have followed an acute infection, puerperal fever, gonorrhea, etc.; and in No. V. of my series the patient had recently had gonorrhea, and in Nos. XXI. and XXIX. there had been otitis media. The rheumatic poison is probably responsible for very many cases. But in a very large group the condition persists for so many years, as in Cases II., XIV., XV., and XXVII., that an acute infective process is out of the question.

The visceral lesions are most diverse in situations and form, and vary a good deal with the character of the eruptions. It has to be borne in mind that certain skin lesions are associated secondarily with diseases of the internal organs. Purpura of a severe type is very common in Bright's disease; urticaria and purpura in cirrhosis of the liver and cholelithiasis; urticaria in asthma, and all forms of erythema with the chronic valvular lesions of the heart in children. It may not always be easy to say, particularly in asthma, which is the primary, whether the urticaria has preceded the asthma, or *vice versa*.

The complications form two great groups—the angioneurotic and the inflammatory. To the former belong the swellings of the fauces, the edema of the glottis, the changes in the bronchial mucosa, causing asthma, and the colic, which is probably due to localized edema of the gastrointestinal walls; to the latter the more serious com-

plications, endocarditis, pericarditis, pleurisy, pneumonia, and nephritis, but, as it is not easy to make a sharp distinction in all instances, it will be better to discuss the complications according to the organs attacked.

Cerebral. In two cases there were brain symptoms, active delirium in Case I. at the time of the recurring attacks, while in Case XV. there were five or six attacks of aphasia and hemiplegia, and the cerebral and cutaneous manifestations lasted for thirteen or fourteen years! It seems not improbable that these transient attacks were due to vascular changes in the brain, the counterpart of those occurring in the skin. An analogous condition is met with in Raynaud's disease, of which I have reported a remarkable instance,[1] with repeated attacks of monoplegia, aphasia, and hemiplegia, alternating or occurring at the same time with the local syncope or asphyxia of the fingers and toes.

Respiratory. Swelling of the fauces and larynx may cause severe dyspnea and attacks like croup. In the family I described with angioneurotic edema two members died of edema of the glottis. In Case XXV. of the series the lad had much swelling of the fauces and croup-like attack, twice accompanied with swelling of the throat and neck, evidently due to edema.

The association of asthma with urticaria and other skin diseases of the erythema group has long been known, and one of the last papers of our lamented friend Dr. F. A. Packard dealt with this subject.[2] It seems to be most frequent with urticaria. There was no instance in my series, though in Case II. there was a persistent catarrh of the smaller tubes leading to emphysema.

Three of the patients had severe pneumonia. In Case II. it occurred toward the close of the remarkable illness of five years' duration. In Case XI. the child died of croupous pneumonia a month after the onset of the third attack of purpura. It was impossible to say whether there was any connection between the two diseases. In Case XXVI. there was a protracted pneumonia following directly upon a severe outbreak of exudative erythema. It is likely that the recurring skin lesions, the pleuropneumonia, the phlebitis, the general glandular enlargement, and the fatal nephritis were due to one and the same poison.

[1] American Journal of the Medical Sciences, 1891.

[2] Ibid., 1896.

Cardiac. Acute endocarditis seems a rare complication. I saw an instance in Philadelphia, and there are a good many cases in the literature, usually in the intense arthritic purpura (peliosis rheumatica). Only three cases in my series had heart murmurs, and in none of the patients was it likely that endocarditis existed. Pericarditis occurred as a terminal event in Case II.

Gastrointestinal Symptoms. One of the most constant features in this whole group, occurring in twenty-five of the cases, is the recurring attacks of colic, sometimes with vomiting, sometimes with diarrhea, occasionally with the passage of blood. The association of attacks of colic with outbreaks of urticaria has long been known. Analyzing the series here reported there were eight cases in which the colic occurred alone with the outbreak of the skin lesions; in fifteen there were in addition gastric attacks, nausea and vomiting, and in five diarrhea, and in eight blood occurred with the colic. The colic is severe, and the attacks may persist for an hour or more and may require morphin for relief. The diagnosis of renal colic was made in one case (Case II.), and in Case XX. the patient was admitted to the surgical ward for appendicitis. Two interesting associations of the colic may be referred to here. In certain cases of angioneurotic edema, a malady which belongs to this erythema group, colic is a special feature, and in the family I reported almost all of the cases throughout the five generations had colic with the outbreaks of the edema. Still more interesting is the relationship which this condition bears to those obscure cases of recurring colic and gastrointestinal crises in children, many of which I believe belong to this group. Take, for example, the following case:

Charles E. D., aged thirteen years, referred to me by Dr. Dick, of Salisbury, Md., on February 8, 1903, complaining of attacks of severe cramps in the abdomen, which have recurred at intervals for nine years. At first they occurred every month or two, and were associated with vomiting of green bile. Now he does not vomit. Of late years they have recurred with much greater frequency, so that now he never passes a week without an attack. So far as I can make out there is nothing in the diet which ever makes any difference. He is better in warm weather, and more often has the attacks in damp weather, in winter, and after prolonged exertion.

He never has any diarrhea. He has had swelling of the joints, occasionally has had growing pains and pains about the knees. The attacks begin abruptly. Occasionally he has a little premonition in the way of uneasy sensations. The doctor states that he writhes about on the floor in the attack and doubles himself into a knot and squirms about the floor like a snake. As the father expresses it, the contortions are awful. Last week he had an attack every day, but not of great severity, and this is the rule. Attacks at long intervals are always more severe. The examination of the child was negative. The urine was negative, except that the morning specimen showed a slight trace of albumin. The child was not very well grown, and looked pale and delicate. The spleen was not enlarged.

Naturally I asked particularly about the occurrence of hives or of any other skin rash, or the occurrence of arthritis, but the history was entirely negative. What is particularly interesting about the case is the fact that his mother had similar attacks during her early life, which lasted until she reached puberty. The boy has three sisters, each one of whom suffered in early life severely with hives, but had no abdominal pains.

Cases XVIII. and XXVII. show the connection of this type of colic in children with the condition under discussion. For years there were attacks of colic of great obscurity. In the former case the child was admitted with a typical outbreak of purpura and erythema; in the latter the skin lesions have lately given a clue to the nature of the protracted abdominal attacks. In angioneurotic edema the patients may have colic alone without the giant urticaria. In children recurring colic with nausea and vomiting may be sometimes a gastrointestinal counterpart or equivalent of a cutaneous attack, as they certainly are in angioneurotic edema, and, as I think, we may take it for granted they were in Cases XVIII. and XXVII.

Renal. In fourteen of the cases there was acute nephritis, indicated by albumin and numerous tube casts, and in seven cases blood. In Case VII. there was albumin without any blood or tube casts. In two cases the picture was that of an acute nephritis with dropsy. The seriousness of the nephritis is shown by the fact that of the seven deaths among the twenty-nine patients five died of uremia. The importance of the poisons causing the skin lesions of

the erythema group is not sufficiently recognized as a cause of acute nephritis. Dickinson makes no mention of it in his article in Allbutt's *System*, and in most of the other systematic writers there is a corresponding silence on the subject. The nephritis, as a rule, comes on at the height of the skin lesion, or it may follow within a week or ten days, or even, as in Case XXVI., a couple of months after the subsidence of the skin lesion. There may be no dropsy even with an intense nephritis (Case II.). The edema of the skin lesion may simulate the puffiness of the face in renal dropsy. This was very marked in Case XXV. The photograph sent by Dr. Love showed a typical renal facies, but in this boy the urine had never been albuminous. Five of the fourteen cases of nephritis died with uremic symptoms. With reference to the skin lesions in the renal cases, in four purpura alone was present; in three, purpura and urticaria; in two, purpura, urticaria, and erythema; in one, purpura, erythema, and edema; in one, at various times purpura, simple erythema, urticaria, and localized edema were present; in one, edema and erythema, and in two, purpura and erythema. Purpura was the most constant lesion, occurring in thirteen of the fourteen cases with nephritis. It is interesting to note that there was not an instance of nephritis with edema alone, and I have never met with it in pure cases of angioneurotic edema.

The morbid anatomy of this type of nephritis has not been very carefully studied, and I had no postmortems on any of the fatal cases in my series. Dr. W. T. Watson,[1] of Baltimore, has reported a remarkable case in a girl, aged ten years, who had had for two or three months transient pains in the abdomen. On the evening of January 28th she had a chill, followed by vomiting and fever; on the 31st, patches of erythema and maculæ; on February 1st, arthritis; on February 2d, purpuric spots; on February 3d, acute nephritis. On March 1st there was an aggravation of the condition with blood in the urine. On March 5th there was almost complete anuria, followed by general anasarca and death on the 12th. There was no endocarditis. The spleen was enlarged and firm. The kidneys were immensely enlarged, measuring each 12 x 7 cm. The cortices were pale, the striations distinct, the glomeruli promi-

nent as gray, transluent nodules, almost like miliary tubercles. There were some small hemorrhages. Dr. W. McCallum, who made the autopsy, reports that microscopically the kidney shows extensive degeneration in the renal epithelium. Many tubules are partly filled with desquamated and degenerated epithelial cells, while the lining of others is ragged and shows fatty change. The tubules contain, besides the desquamated cells, many hyaline casts, or are sometimes filled with red blood corpuscles. The glomeruli form the most striking feature in the section. The Malpighian tuft is in almost everyone much compressed by the new-growth of a mass of cells in the area of the capsular space which forms a crescentic mass. These cells lie in a connective tissue network, which is continuous with the connective tissue outside the capsule. They have often small, subdivided, capsular spaces lined by capsular epithelium, suggesting that the original capsular space was merely invaded by this new-growth. Dr. McCallum tells me that the case belongs to a group which has been lately described under the name of adhesive glomerulonephritis, in which there is not only a proliferation of the epithelial cells, but also a new-growth of connective tissue in the capsules.

Arthritis or arthritic pains were present in seventeen cases. The joint lesions were slight, as a rule; in no case was there severe polyarthritis. The relation of the rheumatic poison to the arthritis and the other lesions is clear enough in some cases, but we cannot say that the arthritis is a hall-mark by which we can always recognize the rheumatic poison. A great many of the cases of arthritic purpura or the peliosis rheumatica have, I believe, nothing to do with the poison of rheumatism. On the other hand, erythema, with or without purpura and arthritis, may be in children, as are endocarditis, tonsillitis, and subcutaneous fibroid nodules, manifestations of the rheumatic poison—links in the rheumatic chain.

Hemorrhages from the Mucous Membranes. There may be recurring severe attacks of expistaxis, as in Case X.; more frequently they are slight. With the colic blood may be passed, usually in small amounts; it occurred in seven cases. Blood was passed with the urine in eight cases, in all in association with nephritis. In Case XIV., after outbreaks of urticaria for years, the final symptoms were those of a severe purpura hemorrhagica.

List of Cases with Visceral Lesions of the Erythema Group.

No.	Name.	Age and sex.	Skin lesions.				Fever.	Colic.	Vomiting.	Diarrhea.	Hemorrhages.	Nephritis.	Albumin.	Arthritis or arthritic pains.	Endocarditis.	Enlarged spleen.	Other complication.	Mode of death.	Duration.	Remarks.
			Purpura.	Urticaria.	Edema.	Erythema.														
1	B. L.	M. 27	...	...	...	1	1	1	1	...	.....	...	...	...	...	1	.....	.....	6 yrs.	Delirium in attacks.
2	W. E. B	M. 11	1	1	1	1	...	1	...	...	Nose.	...	...	1	...	1	Bronchitis, cough, emphysema, pneumonia.	Pericarditis.	5 yrs.	
3	I. W.	M. 6	1	1	...	...	...	1	...	1	Bowels.	1	1	1	...	...	.....	Dropsy & uremia.	10 wks.	
4	B. H.	M. 46	1	1	...	...	...	1	1	1	.....	1	1	1						
5	J. D.	M. 38	1	1	...	1	1	1	1	...	Urine.	1	1	1	...	...	Gonorrhea.	.....	2 mos.	Came on after gonorrhea.
6	W. L.	M. 9	1	...	...	...	1	1	1	...	Bowels.	1	1	1	...	...	.....	Pneumonia.	Third attack.	Death from pneumonia a month after onset of third attack.
7	W. R.	F. 4	1	1	1	...	1	1	...	...	.....	...	1	1	...	...	.....	.....	About 3 wks.	
8	O. L.	F. 5	1	...	...	...	...	1	...	1	Urine.	1	1	1	...	...	.....	Uremia.	.....	General anasarca.
9	L. J.	M. 12	1	1	...	...	...	1	1	...	.....	...	...	1	...	...	.....	.....	.....	Remarkable case; symptoms like purpura hemorrhagica.
10	B. W.	M. 30	1	1	...	...	...	1	1	...	Nose, recurring attacks; gums.									
11	A. R.	F. 18	1	1	...	...	...	1	1	...	Stomach, bowels, lungs.	...	...	1	...	...	.....	.....	4 yrs.	Recurring attacks of great severity.
12	B. L.	F. 24	...	1	...	1	1	1												
13	R. B.	F. 49	...	...	...	1 exnd.	1	1	...	...	.....	...	...	1	...	1				
14	A. D.	M. 57	1	1	...	...	...	1	1	...	Stomach, bowels, urine.	1	1	...	...	..	Bronchitis.	Uremia.	27 yrs.	Extraordinary case; hemorrhages in final attack.

15	C. A. R.	M. 29	1	1	1	...	...	1	...	..	Urine.	1	1	...	...	...	Aphasia and hemiplegia, 5 or 6 attacks.	.....	13 to 14 years.	Remarkable case.
16	H. L.	M. 11	1	...	...	...	...	1	1	...	....	...	...	1						
17	G. K.	M. 18	...	1	...	1	...	1	...	...	....	...	...	1	Apex mur.					
18	B. P.	F. 7	1	...	...	1	1	1	1	...	Bowels.	...	...	1	...	1	.....	.....	.....	Remarkable case; recurring colic for five years; case like No. 26.
19	E. C.	F. 15	...	...	1	1	1	...	...	...	.....	1	1	...	...	1	Otitis, enl. lymph glands.	Uremia.	7 mos	
20	M. R.	M. 15	1	1	...	1	...	1	...	...	Bowels. urine.	1	1	...	...	1	.....	.....	.....	Admitted for appendicitis.
21	J. D.	M. 12	1	...	...	...	1	1	1	...	Urine.	1	1	...	...	...	Otitis.			
22	E. C.	F. 6	1	1	...	...	...	1	...	...	Urine.	1	1	1						
23	S. E. W.	F. 14	1	1	...	1	1	1	1	1	.....	.	...	1	1 mur.	1				
24	M. S.	M. 3	1	...	...	1	...	..	...	...	.....	1	1							
25	N. D.	M. 14	...	1	1	1	...	...	...	...	.. ...	...	...	...	...	...	Swelling of throat, edema of face, spasmodic croup.	.....	.....	Remarkable case.
26	L. E.	F. 24	1	...	...	1	1	...	...	...	.....	1	1	...	...	...	Pneumonia, thrombosis left femoral vein, enlargement lymphatic glands.	Uremia.	8 mos.	Extraordinary case, like No. 19.
27	D. B.	F. 13	...	1	...	1	1	1	1	...	.....	...	...	...	Syst. mur.	...	.....	.....	.....	Colic from infancy.
28	A. S. A.	M. 26	1	...	...	...	1	1	1	1	Bowels.	...	...	1						
29	E. F.	M. 5	1	...	...	...	1	1	1	...	Bowels.	1	1	1	..	...	Otitis media.			

Lastly, it is of interest to tabulate the cases according to current nomenclature of skin diseases. In five purpura was the only lesion; in four, with arthritis; four, with fever. In seven there was the common combination of purpura with raised wheals—purpura urticans—which is the usual lesion of peliosis rheumatica. In five cases there was angioneurotic edema, sometimes occurring alone, more frequently with other erythematous lesions, or alternating with them. Erythematous lesions occurred in fourteen cases, in only two alone, with swelling in the form of erythematous blotches, usually with purpura or urticaria, once only with vesiculation of an extensive character.

A word as to treatment. The very chronic cases with recurring colic for years may resist all measures. Alterative courses of gray powder, with careful dieting, may be helpful. With angioneurotic edema nitroglycerin in full doses may be tried. Dr. Love writes that in his remarkable case (No. XXV.) camphor has done good. In such severe types as Case XIX. nothing seems to arrest the progress. The chief danger is from the kidneys, and in so frequently presenting this subject I have hoped to impress upon my colleagues the importance of recognizing this form of nephritis, and of taking early precautions to prevent its progress, against which I think protracted rest in bed and a milk diet are the best means at our disposal.

PRIMARY CANCER OF THE LUNG.

By J. H. MUSSER, M.D.,
OF PHILADELPHIA.

During the past eighteen months three cases of cancer of the lung have come under the observation of the writer. The diagnosis of two was verified by autopsy; the clinical course of the third seems to be conclusive. The first case was one of massive tumor of the lower lobe of the right lung, with a few scattered nodules in the other lobe, and metastases in the liver and the lymph nodes of the thorax. It is referred to in the article on cancer of the lung, fourth volume of the system of medicine of Nothnagel. No further reference will be made to it in this paper except to repeat that the clinical course and physical signs were those of a pleuropneumonic infection. Pain was the first symptom, but it soon disappeared. Signs of effusion were present, but aspiration and exploration were negative, the latter revealing the nodule in the lung. Fever of moderate degree, 101° at the highest, with well-marked leukocytosis, was present throughout the disease. Cachexia did not appear until very late. The liver involvement was shown by a large non-fluctuating mass, which grew rapidly. The duration was less than three months. The patient was a male, aged forty-nine years, in whose family, social, and previous medical history there was nothing suggestive.

The second case will be the subject of this report. The third was a male, aged seventy-one years, who had a cough for six months; loss of flesh and strength; a very large pleural effusion of three weeks' duration, which, when aspirated twice, did not lessen an area of dulness in the left axillary and post-thoracic region. The fluid was very bloody, but did not show any cellular elements suggestive of carcinoma. Aspiration was performed twice. Prostration and emaciation continued. The supraclavicular and cervical lymph nodes on the left

side enlarged and became indurated, seeming like secondary metastases. Removal for examination was not permitted. Death took place from asthenia at the end of nine months from the appearance of the effusion. The involvement of the lymph nodes seemed to prove the nature of the process to be carcinoma.

The case which is the subject of this report was of special interest because of its rapid course, its unusual onset, its resemblance, clinically, to tuberculous bronchopneumonia, and the resemblance of the lesions, macroscopically, to that process. Indeed, until sections were made it appeared to the naked eye to be a diffused, caseous pneumonia of tuberculous origin.

Case.—H. B., aged forty-seven years, clerk, single; residence Pennsylvania; consulted me December 12, 1902. Not closely confined and duties not arduous; no exposure; habits regular. Eats hurriedly; smokes moderately; no alcohol; moderate tea and coffee.

Always healthy; no syphilis. At fifteen years had injury to knee the effects of which entirely disappeared. Had a very severe attack of influenza in 1890; dysentery in 1902. Weight ten years ago, 165 pounds. Family history excellent.

Present Condition. Complains of indigestion, sore throat at night, expectoration of mucus, dyspnea on exertion, loss of flesh, and weakness. The gastric symptoms and sore throat continued since the attack of dysentery in August. The expectoration has been increasing for four months. The loss of flesh has been noted for three months.

The special characteristics of the symptoms must be noted. The sore throat was present at night, and even then only in the recumbent posture. In the day, if he would lie down, it would return, to be relieved immediately on rising. The expectoration was remarkable. A moderate cough would be attended by the welling up of large amounts of fluid, so that when I saw him spitting was one of the most distressing symptoms. Indeed, cough did not by any means bring up the fluid; it simply welled up from the pharynx and esophagus. The patient estimated that three pints were discharged. Headache was more or less constant, but only when the patient was coughing. Dyspnea has been progressively increasing the past month. Sleeplessness has been a very distressing symptom.

Physical Examination. Fairly well nourished; sickly appearance; anxious expression; voice clear, but weak; skin normal; no eruptions; no edema; tissues flabby; weight, 140 pounds; temperature normal; slight enlargement of right lobe of thyroid gland; eyes normal.

Heart normal size; sounds normal; action rapid; pulse, 110 to 116, 120 to 130 on exertion; respiration, 28 to 32; no difference of two sides. No signs in lungs, except a slight pleural friction in right axillary region. Resp-

nance skodaic over right base. Nothing unusual on abdominal examination. Stomach tube of good caliber passed without difficulty.

Laboratory Examinations. Sputum clear, mucoid, and slightly purulent; microscopically some pus; no tubercle bacilli; diplococci in moderate numbers. A second specimen same results, except some blood.

Blood. Hemoglobin, 80 per cent.; red blood corpuscles, 4,000,000; white blood corpuscles, 12,000.

Gastric Contents. After test meal 30 c.c., some mucus, small amount of bread. Total acidity, 30; free HCl.

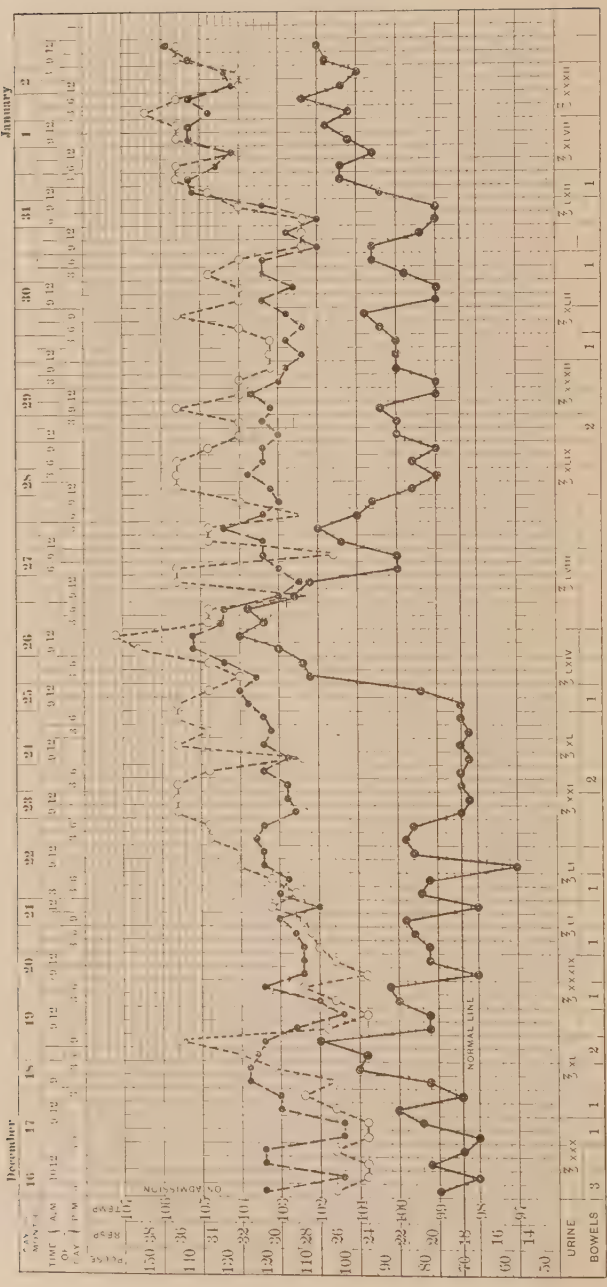
Urine. 1020; no albumin or sugar. Microscopic examination negative.

Nose, Fauces, Larynx. Dr. Bliss says: "There is no infiltration of the larynx suggestive of tuberculosis or syphilis. The entrance to the œsophagus, as nearly as it can be seen, appears normal. There is no bulging forward of the posterior wall of the larynx or trachea suggestive of a new-growth in the esophageal wall. The lymphoid tissue at base of tongue is not in abnormal excess. The entire mucous membrane of nose, nasopharynx, pharynx, and larynx shows considerable catarrhal inflammation, as indicated by proliferation and desquamation of the superficial epithelium, and an excessive flow of thick, tenacious mucus, considerable quantities of which come from the nose and nasopharynx. The action of the vocal cords does not indicate any pressure on the recurrent laryngeal nerves. The interarytenoid space is thickened, but only, I think, as a result of the simple pharyngolaryngitis, not as a result of a specific inflammation or beginning of a new-growth. There seemed to be a very pronounced pulsation of the right carotid in excess of that of the left side."

While under observation from December 12th to December 16th, patient became worse, alarmed particularly about throat, growing weakness, and absolute loss of appetite. On the latter date admitted to University Hospital.

The accompanying temperature, pulse, and respiration record shows the course, as far as these symptoms are concerned, and the rapid progress of the disease.

December 16, 1902. Physical examination by Dr. Sailer. There is slight prominence of precordium; sternum is slightly funnel-shaped; the intercostal spaces distinct; pulse small, rhythmic. Apex-beat is weak, circumscribed, fifth interspace in nipple line. No diastolic shock; no cardiac impulse. Area of cardiac dulness diminished. Heart sounds are clear, but faint; there are no murmurs, bruit, etc., audible on both sides of neck. There is a faint, suprasternal pulse, a diastolic venous pulse in neck; no evidences of atheroma. Lungs anteriorly are negative; posteriorly the resonance extends an inch lower on left than on right. The breath sounds are harsher on right side, and vocal resonance more distinct; there is a to-and-fro friction sound over left base posteriorly. The lower border of liver extends about an inch below costal margin. Spleen is not palpable; no tenderness; kidneys not palpable. Knee-jerks are slightly diminished,


December
January
NORMAL LINE
PULSE
RESP.
TEMP.

Breath sounds are quite indistinct in expiration; markedly rhoncous in inspiration, and attended by an abundance of small frictions on right side. Feeble breath sounds at right base, with frictions.

Urinalysis. Yellow, clear; specific gravity, 1025; alkaline; albumin, sugar, bile, and indican negative. Amorphous phosphates; triple phosphate crystals.

Blood. Hemoglobin, 95 per cent.; red blood corpuscles, 5,250,000; white blood corpuscles, 10,740.

17*th.* Physical signs of pleuritis and diffused bronchitis.

19*th.* Bronchial breathing in right base.

24*th.* Bronchial breathing and moist râles heard at both bases. Sore throat. Dyspnea extreme; sleepless; much agitation; no appetite. Sputa shows three layers, as in bronchiectasis.

25*th.* White blood corpuscles, 26,280. No pain. Dyspnea and sore throat continue.

27*th.* White blood corpuscles, 21,480. Severe conjunctivitis. No tubercle bacilli in sputum; many diplococci. Culture from throat taken by Dr. Evans: "Growth of staphylococcus pyogenes aureus, together with bacteria, common to mouth and non-pathogenic in character. Special attention was paid to the possibility of the presence of the bacteria of influenza and diplococcus pneumoniæ, but the methods used for the growth of these failed to reveal their presence." Culture from eye: "Pure culture, staphylococcus pyogenes aureus."

28*th.* No tubercle bacilli in sputum; many diplococci pneumoniæ. White blood corpuscles, 19,600.

31*st.* White blood corpuscles, 14,900. No change except aggravation of symptoms; progressive exhaustion; orthopnea; anxiety; pain in throat.

January 1, 1903. White blood corpuscles, 21,600. Sputum showed no tubercle bacilli on repeated daily examinations; showed diplococcus of pneumonia since December 28th, also streptococci and staphylococci. No bacillus of influenza demonstrable. Patient has coughed a great deal the last two days. Expectoration has been free, and settled in three layers in a conical glass; frothy and turbid on top, clear in the middle, and a heavy white precipitate at the bottom. The dyspnea has increased markedly the last two days, and has been greatly aggravated by coughing spells.

2*d.* White blood corpuscles, 26,330. Patient spent a fairly comfortable night under the influence of frequent hypodermics of heroin. He has a constant tickling in the throat and a great dread of a coughing fit.

3*d.* At 4 A.M. pulse was 134 and rather weak, and his condition was that of collapse. Shortly after this time his breathing became much more labored, and he died at 5.30.

Autopsy, January 3, 1903, by Dr. R. M. Pearce.

Anatomic Diagnosis. Primary epithelial tumor of both lungs; metastasis in cervical, tracheal, and bronchial and retroperitoneal lymph nodes; fatty degeneration of liver, kidneys, and myocardium; chronic thickening of

spermatic cord; cystic degeneration of thyroid; chronic splenitis; acute catarrhal bronchitis and tracheitis.

External Appearance. Body that of a well-developed, emaciated male. Old scar over left tibia. Subcutaneous fat greatly diminished in amount; muscles pale.

Abdominal Cavity. No fluid; no adhesions. Appendix normal. Retroperitoneal lymph nodes enlarged to the size of from one-half pea to one-half bean; glistening white in color; no caseation. Gastrohepatic lymph nodes somewhat enlarged in size, reaching the size of a hazelnut, but not caseous.

Pleural Cavities. Small amount, about 50 c.c., of slightly cloudy serous fluid in either. Here and there attached to the visceral surface of pleuræ are a few fine flecks of fibrin. The lymphatics beneath the pleuræ are greatly dilated.

Pericardium. Normal amount of fluid; surface normal, except for a white patch over the right ventricle near base.

Heart. Valves and cavities normal. Myocardium soft, flabby, and on section reddish-gray in color, with coarser streaks of gray throughout.

Lungs. Uniformly throughout both lungs, affecting all parts, is a diffuse, grayish-yellow infiltration. At the periphery of the lungs this infiltration appears to a certain extent in the form of discrete areas 0.3 cm. to 0.5 cm. in diameter beneath the pleuræ. Except for this discrete peripheral distribution, the process is uniformly confluent, and exhibits a uniformly grayish-yellow, opaque appearance. Here and there are found a few older, softened areas of small size and of a distinctly yellowish color. Bronchial and tracheal lymph nodes are enlarged to the size of a pea, smooth and glistening, and on section show no caseation.

Pancreas. Small, firm; on section trabeculæ prominent, pulp dark-red in color.

Stomach and Intestines. Normal throughout.

Liver. Capsule smooth, grayish red in color, and on section very marked fatty degeneration of the periphery of the lobules, the centers appearing as reddish dots. Gall-bladder normal.

Kidneys. Capsule peals readily; surface smooth. On section cortex very pale, grayish in color; glomeruli distinct. Pyramids injected. Adrenals normal.

Bladder, prostate, and seminal vesicles normal.

Testicles and epididymis normal.

Spermatic cord shows slight glistening, fibrous thickening, without, however, any evidence of tuberculosis or caseation. This condition affects both cords.

Aorta. Smooth throughout.

Organs of Neck. Esophagus normal. Trachea and larynx injected and contain a considerable amount of mucus. Glands of the neck slightly enlarged and similar in appearance to the glands elsewhere. Thyroid in the lower portion of the right lobe contains a few small cysts from 2 mm. to 4 mm.

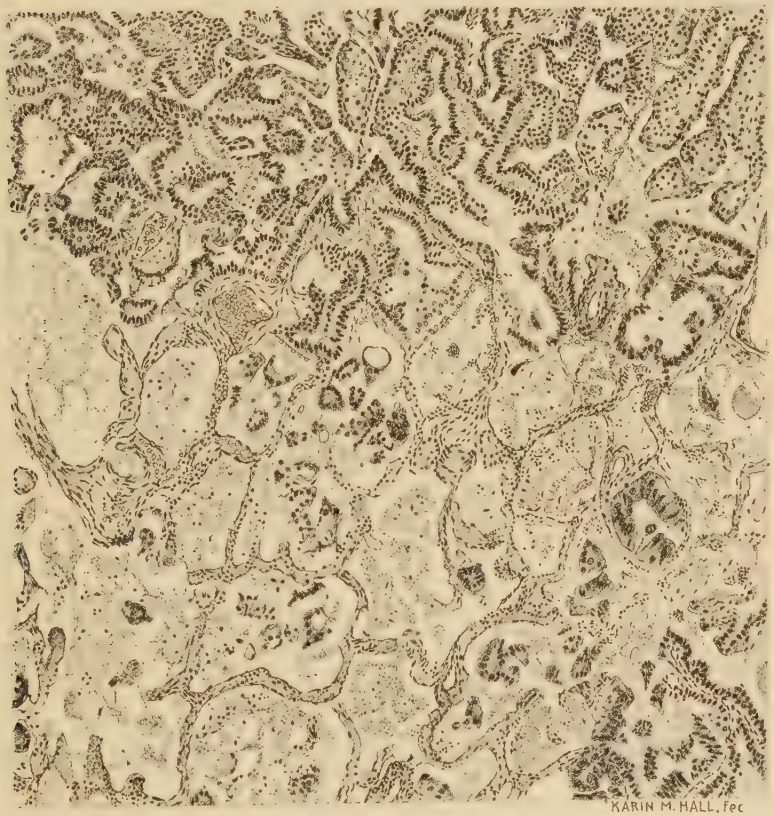
in diameter, containing clear, gelatinous material. Other portions of thyroid normal.

Head. Not examined.

Cultures from heart's blood, liver, spleen, and kidneys sterile.

Histologic Description of Tissues. A superficial examination with the lower power of the microscope reveals a diffuse epithelial growth in which the

FIG. 1.

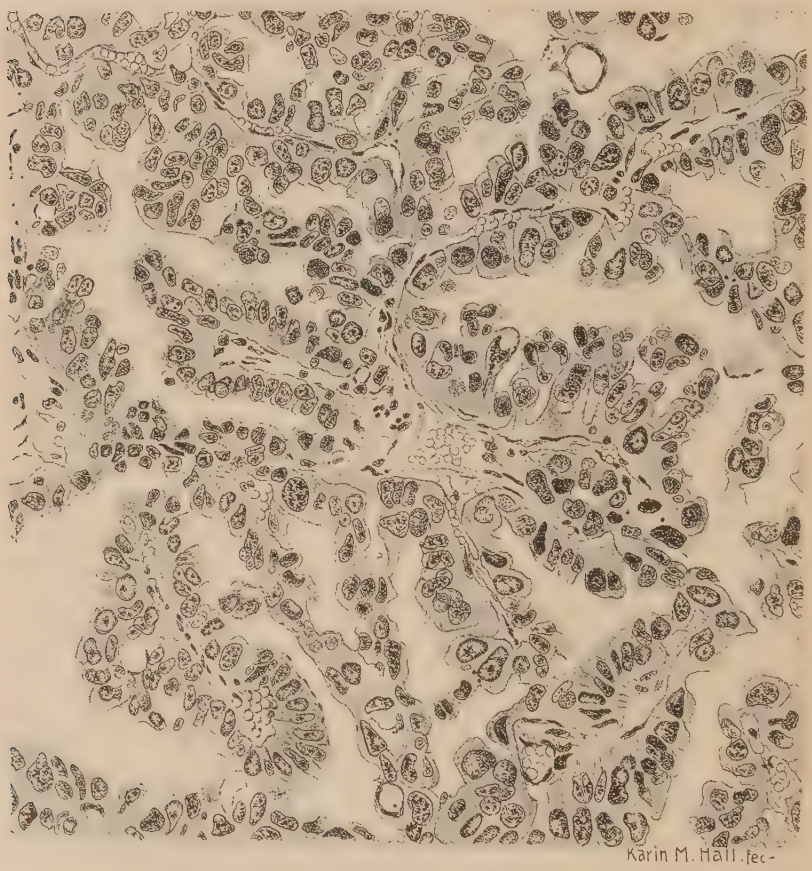


Low power. Advancing portion of tumor. Above, solid tumor with tendency to papillary arrangement; below, alveoli containing coagulated serum and small tumor masses apparently originating in epithelium of air cells.

general alveolar appearance of the lung is more or less retained. Areas of necrosis are not infrequent. In these areas, which are infiltrated with leukocytes, the outlines of tumor masses are still visible. In the neighborhood of such necrotic areas small accumulations of serum and fibrin are found.

Upon detailed examination the character of the tumor is found to vary in its different portions. In the younger portions, where tumor is in contact with normal alveoli, the cells form a definite, peripheral, ring-like arrangement corresponding to the inner surface of the alveoli. These cells are in

FIG. 2.

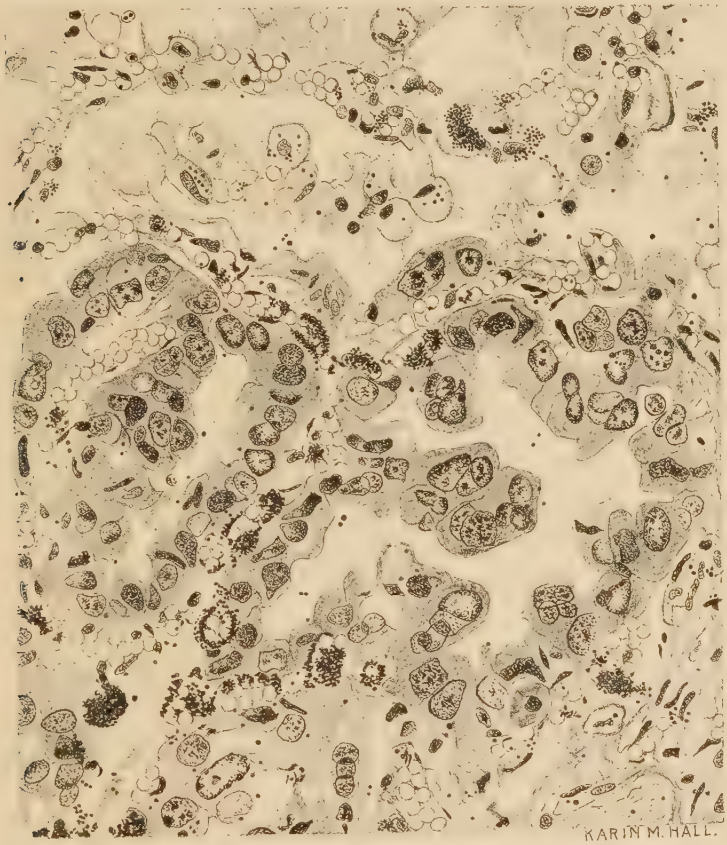


High power, showing arrangement of cells about alveolus-like spaces and tendency to papillary growth.

part flat, with much protoplasm and with vesicular nuclei corresponding to alveolar epithelium, and in part are pressed together to form giant-cell-like masses, with distorted and irregular nuclei. Stalk-like processes are occasionally seen to protrude into the alveolar space. Such stalk-like processes vary from those containing four, five, or six cells to large masses, completely

filling alveolus. In more compact portions of tumor the cells lining the alveoli may assume a cylindric shape. In these earlier portions of the tumor the only stroma is that of the normal framework of the lung. Alveoli along advancing edge not filled with tumor cells contain granular and disintegrated desquamated cells.

FIG. 3.



High power, showing transition of cells of alveolus.

In older portions of tumor the arrangement of the tumor is distinctly papillary, the cells somewhat cylindric, and the stroma increased in amount. At first glance this portion of tumor seems to bear no relation to the earlier portion, but on careful study it is seen that the stroma and the bloodvessels bear a close resemblance to the normal interalveolar wall. The papillary processes can in nearly all instances be shown to lie in spaces, their point of

origin being from cells lining the stroma. The picture is, therefore, one of proliferation of cell lining the alveoli, the proliferating cells assuming, owing to the restraint under which they are placed by the limiting alveolar wall, a papillary arrangement and filling the alveolar space. As a result of the increased demand of this new tissue for nutrition, a greater vascularization of the alveolar wall has occurred with corresponding increase in stroma. The occasional presence of carbon pigment in the stroma is evidence that the stroma is not entirely a new formation.

The epithelium lining bronchi of all sizes is intact. The mucous glands show no deviation from normal. In loose tissue about the lymphatic spaces of the bronchi the extension of the tumor is seen in the form of a tubular arrangement of the epithelial cells entirely distinct from the cylindric cell of the bronchial epithelium. The bronchi are filled with desquamated cells, leukocytes, serum, and red blood corpuscles.

The necrosis is of the type of coagulation necrosis, with for the most part preservation of the form of the cell; occasionally, however, complete destruction is evident. Leukocytic infiltration is extensive. Examination for tubercle bacilli gave negative results.

The metastases in the bronchial, tracheal, and cervical lymph nodes are of the same character as in the older portions of the tumor in the lung. The stroma is abundant, the papillary arrangement distinct, and the cells tend to take an indefinite cylindric form. That the stroma is that of the lymph wall greatly thickened is shown by the presence of carbon pigment. Only a few islands of normal lymphoid tissue remain. In nodes most involved the growth is most abundant at the periphery, apparently extending along the sinuses toward the center. No necrosis is seen in these metastases.

Thyroid. Examination of cystic portion of thyroid shows dilated alveoli, which are filled with colloid material. There is no atypical arrangement of the lining cells.

Spermatic Cord. Fibrous thickening about vas deferens; lumen of vas is patent, though constricted, and contains desquamated epithelial cells; the lining epithelium is quite intact.

Examination of other organs of no particular interest.

Diagnosis. Primary carcinoma of the lung originating in alveolar epithelium.

Remarks.—It was difficult for the writer to explain the *sore throat*, insomuch as the pain was out of proportion to the local lesion, and, moreover, that it was worse in the recumbent position was another unusual phase. It seemed possible there was an undemonstrable intrathoracic pressure which in some way increased the congestion and pain. Such pressure would also have explained the unusual *dyspnea*. No other cause for the dyspnea could be found and no other explanation, except that of miliary tuberculosis.

The very pronounced flow of mucus—the excessive *expectoration*—was a feature of great interest. Remembering well the late Dr. Harrison Allen's paper upon the occurrence of this symptom in malignant disease of the esophagus, with intrathoracic tumor to explain the above noted symptoms, this affection was sought, but with negative results. The only other explanation that occurred to the writer for the excessive fluid discharge was the occurrence of bronchitis due to tuberculosis. The possible occurrence of this infection seemed to explain the rapid pulse, rapid respiration, orthopnea, emaciation, loss of appetite and of strength. The onset of signs of bronchopneumonia supported this view. The change in the physical characteristics of sputum, so that one could surmise a bronchiectasis, was in accord with this view, as such bronchial dilatation will be found in the diffused bronchitis of tuberculosis. Against tuberculosis was the negative findings on examination for bacilli. (The guinea-pigs did not succumb to tuberculosis, although sufficient time after inoculation had not elapsed to make this a diagnostic point.) If the writer had maintained that tuberculosis was not proven as bacilli were not found, no positive diagnosis would have been made. The clinical course, the rapid progress, the rapid pulse, the thoracic symptoms and signs, it seemed to the writer, could alone be explained by this infection.

The diagnosis of carcinoma of the lung was not made for the reasons mentioned. In the light of the autopsy we can now explain the symptoms which were out of proportion to physical signs, early at least in the affection. The rapid breathing, the rapid pulse, the severe orthopnea, the excessive expectoration, all had their origin in the diffused lesion with which we were confronted at the autopsy. Stenosis of the smaller divisions of the bronchi was produced by the great epithelial proliferation.

Of interest, too, during life was the enlarged thyroid, which proved to be cystic, suggesting an explanation for the rapid pulse.

It may be noted that the cases herein reported swell the large proportion of males to females already commented upon by writers.

Finally, it may be worth recording, had we put more faith in the examination of the sputum, which always was against tuberculosis, we would have at least not made a positive diagnosis from which there was no retraction.

On the other hand, too much stress in both cases was placed upon the *leukocytosis*. Not that its presence counted for or against tuberculosis, the latter in uncomplicated cases. Here, indeed, it could be said, the leukocytosis was against tuberculosis, which should have some weight, although we held, and it was no doubt true, the blood change was due to a mixed infection. In the first instance the increase of white cells in a supposed pleural infection was thought to be due to a small empyema, perhaps on the diaphragm, upheld for a long time by the clinical course.

To summarize, it may be said the case is of interest because—

1. Of its rarity.
2. The complete clinical and pathologic study.
3. The apparently simultaneous involvement of almost the entire extent of *both* lungs (almost complete involvement of one lung is not uncommon).
4. Evident origin from epithelium of alveoli. Most of the cases described in literature have arisen in bronchial epithelium. Very few (see Nothnagel) writers ascribe origin to alveolar epithelium. The illustrations (high power) are an attempt to demonstrate this origin.

A DESCRIPTION OF THE BRAINS AND SPINAL CORDS OF TWO BROTHERS DEAD OF HEREDITARY ATAXIA.[1]

Cases XVIII. and XX. of the Series in the Family Described by Dr. Sanger Brown.

By LEWELLYS F. BARKER, M.D.,
of Chicago.

(with a clinical introduction by dr. sanger brown.)

The valuable material which forms the basis of this study was presented (for investigation) by Dr. Sanger Brown, of Chicago, to Dr. William H. Welch, Professor of Pathology in Johns Hopkins University, who kindly turned it over to me. I wish to express my thanks to both these gentlemen for the opportunity they have given me of studying the pathologic changes in a disease so rarely met with.

The description of the anatomic findings will be preceded by a clinical introduction by Dr. Sanger Brown.

Clinical Introduction by Dr. Sanger Brown.

As an introduction to Dr. Lewellys Barker's anatomic report, and for the purpose of facilitating correct deductions therefrom, as well as for the convenience of those interested who have either not read or do not now distinctly remember my clinical report of the series first published in 1892 in *Brain* and in the *North American Practitioner*, I shall undertake to supply some data intended to give a general idea of the characteristic clinical features, together with a

[1] The plates and figures referred to in the text are not published in the Transactions, but will be found accompanying the simultaneous publication of the article in the Decennial Publications of the University of Chicago, vol. x., 1903.

reproduction of my original genealogic chart, showing the hereditary relation of the disease and the age at which it first made its appearance in the individuals affected. Finally, I shall furnish a more particular history of the cases supplying the material for Dr. Barker's report.

From a careful survey of all the cases comprised in the series, I presented in my original paper a general summary, which I here quote:

"Taking these cases alone for a text, and assuming them to be cases of hereditary ataxia, the following diagnostic criteria might be fairly deduced:

"Hereditary ataxia is a disease which may be traced through several—at least four—generations, increasing in extent and intensity as it descends, tending to occur earlier in life and to advance more rapidly. It usually attacks several members of the same family. It occurs most frequently between the ages of sixteen and thirty-five, but it may begin as early as eleven and as late as forty-five. It shows no marked preference for sex, but it descends through females four times as frequently as through males. Atavism rarely occurs. The influence of an exciting cause can rarely be demonstrated, but in some instances a fall or injury has appeared to determine the onset; and any cause like childbearing or lactation, which very much depresses the vital forces, may produce a rapid advance of all the symptoms. There is always considerable incoordination of all the voluntary muscles, and a sluggishness of the movements which they produce, when the disease is well established. This is usually noticed first in the muscles of the legs, but in a few months or years extends to the arms, face, eyes, head, and organs of speech. Sometimes it occurs first in the upper extremities, and sometimes in the organs of speech.

"The ataxia is often extreme and the gait devious, the patient deviating several feet on either side of the intended line of progression before he loses the power of walking. The ataxia is not markedly increased by closing the eyes. The sense of posture is perfect.

"Some weakness of the muscles of the legs, without atrophy, is frequently an advanced symptom, and occasionally [in the late stages] there is permanent spastic contraction of the legs. In developed cases there are usually extensive choreiform movements of the

head, and often of the arms, accompanying all voluntary movements. These irregular movements occur in the hands, legs, or head whenever it is attempted to maintain either of these parts in a fixed position by a voluntary muscular effort. Movement ceases during sleep. The pulse rate may be increased to 112 in advanced cases or may be normal.[1]

"There is usually some degree of static ptosis, with overaction of the levator on looking upward. In rare cases there may be temporary diplopia, in the early stages, due to weakness of the external [lateral] rectus. There is no nystagmus of any kind.

"Atrophy of the optic nerve is a constant and early symptom, and usually progresses slowly with the other symptoms. Rarely it begins earlier in one eye than the other.

"The response of the iris to light and accommodation is sluggish and diminishes with the advance of the optic nerve atrophy; when this latter is complete, as may happen in advanced cases, there may be complete internal and external ophthalmoplegia.

"There is always marked disturbance of the articulation, probably due to inco-ordination of the muscles concerned, for weakness cannot be demonstrated. In some cases there is a troublesome tendency to strangulation in swallowing liquids, due to their getting into the larynx, but otherwise swallowing is in no way difficult.

"Occasionally the sphincters are slightly but positively affected, this symptom appearing only in those cases where spontaneous pains in the legs coexist, having some of the characteristics of those occurring in locomotor ataxia. Excepting the spontaneous pains already mentioned, there is no disturbance of sensibility. There are no vasomotor or trophic symptoms, but there is a marked tendency to emaciation; there is no hypertrophy or valvular lesion of the heart.

"The knee-jerk is always exaggerated, and there is frequently ankle clonus, and the cutaneous reflexes are also always exaggerated, but to a less degree. The exaggeration of the reflexes is an early symptom, and they often decline considerably when the disease is far advanced.

[1] I am inclined to attribute the pulse-rate noted by Dr. Bridge to emotional disturbances, because I have made repeated examinations in the six cases under my care and found it only subject to normal variations.

"There is never paralytic club-foot, nor any other deformity excepting rarely permanent spastic contractions of the legs in advanced cases. In none of these cases have the patients ever suffered from rheumatism so far as I can learn.

"I wish to repeat that the above summary of the symptomatology of hereditary ataxia is only intended to apply to this particular series of cases; and I have only presented it in this way so that it might be the more easily compared with other series."

I shall now quote from my original paper the clinical notes of the cases upon which Dr. Barker's anatomic report is founded, indicating any omissions or additions by asterisks and brackets, respectively. As Case XVIII. was the one which first presented itself, the notes may appear somewhat unnecessarily full and circumstantial. In extenuation I beg to state that when the observations were made I felt I was, perhaps, exploring a new territory and naturally wished to establish the clinical landmarks as firmly as possible. To this end, with the kind co-operation of the family physician, Dr. R. L. James, I presented (happily) the two identical cases now under discussion in person before the Neurological Section of the American Medical Association at the 1892 meeting in Detroit, where they were seen by some of the best-known representative neurologists of this country and by Dr. James Taylor, of London.

Clinical Notes on Case XVIII., Made in May, 1891.

"A business man, aged thirty years, single, of temperate habits, good family history, except that his mother became ataxic at about thirty-three years of age, the disease progressing steadily until she died of tubercular diarrhea at the age of forty-eight. The patient was active and vigorous in every way until attacked by his present disease, being rather among the foremost in all athletic sports and school work. His attention was first attracted to this disease while he was working with a surveying party in Texas, and then it was noticed by others before he himself noticed it. At that time he was twenty years old, and the ataxia was manifested by a staggering gait, which was so marked that his chief thought him intoxicated; but now he recollects that at least two years before this, or when

he was eighteen years old, the draughtsmen in the office where he worked complained that he rendered their desks or drawing boards so unsteady when he leaned against them that they could not well go on with their work; and he further distinctly remembers that on a certain occasion at about this time, when in company with other young men in the country, he was quite unable to read the large letters of an advertisement at a considerable distance, though each of his companions could read them with comparative ease. He feels confident that this comparative visual defect had not always existed.

"I should say here that this patient has a good English education, and that his intellectual capacity is above the average, so that, notwithstanding his affliction, he would at the present time be justly regarded as a well-informed man. He feels quite certain, too—and in this he is corroborated by his older relatives who have had an opportunity of observing him closely—that at the age of fourteen years, when his voice underwent the change incident to puberty, there appeared a gradually increasing defect in utterance; his speech was slower and his syllables less definite and distinct than formerly. The ataxia has always been much more pronounced if he was fatigued, and he now remembers that at the age of eighteen years he could not walk in a straight line when very tired.

"There has been some progressive loss of power in the legs from the first, but this has been insignificant throughout in comparison with the ataxia. As already stated, the ataxia was first noticed in the legs and has progressed more rapidly in them than in other situations. But it has been distinct in the arms from a very early period.

* * * * * * *

"At no time has there been any pain or any other disturbance of sensation; neither has there been any muscular wasting, cramp, or trophic manifestations. The sphincters have not been affected, and the patient thinks sexual power has not been more impaired than can be attributed to the general decline in bodily weight and strength, which has gradually supervened in the past six years, the weight having fallen from 136 to 112 pounds in that period.

"I should have stated that a tendency to choke [strangle] while eating has all along been a troublesome symptom.

* * * * * * *

"For several years past vision has progressively failed, so that he could best read in a dim light.

"*The Present Condition.* The patient is considerably emaciated, though he eats fairly and sleeps well. He is of medium size and well formed. The sensibility is normal; the knee-jerk is greatly exaggerated and equal on both sides; there is a slight ankle clonus; the skin reflexes appear in the main normal, but the cremasteric and abdominal are not strongly pronounced. There is marked ataxia in nearly all voluntary movements; so that the patient can walk only when supported by an attendant, and can stand only when leaning against some solid support. Closure of the eyes does not materially increase his difficulty. The gait is such as would usually be described as cerebellar; the patient leans rather backward against his attendant and sways from side to side, and all the time has an uncomfortable sense of insecurity, as if his head must fall backward to the ground. He experiences a distinct loss of power in the legs, which he thinks is even greater than could be accounted for by his general decline in bodily vigor, but the muscles are firm and well developed. All the voluntary muscular movements are slowly performed, and of this the patient is quite conscious. He cannot reach out his hand suddenly to seize any given object. The hand moves slowly and deviates several inches in various directions from the direct line that would normally be taken in such an effort. This tardiness of movement is readily noticed when the patient raises his eyes; on being addressed, or in winking, the eyelids will rise so slowly as to be suggestive of temporary ptosis, but in the end they are raised too high, so that the sclerotic is often so much exposed as to display an expression usually associated with some intense emotion, when in fact the patient is suffering from no emotional disturbance whatever. Though ataxia in the muscles that move the tongue would be difficult of conclusive demonstration, because the normal movements could hardly be definitely described (and the same might be said of the muscles that move the lips), yet a careful observer would see at a glance that the movement of both tongue and lips (especially the former in this case, because a full beard is worn) were far wider in range than usual. There is no difficulty in swallowing, excepting the tendency to choke already noticed, which might be explained by ataxia and tardiness of the

muscles concerned, because no extraordinary effort has to be made, and there is no tendency for liquids to pass out through the nose.

"There is a marked inco-ordination of the various muscles of facial expression, which is easily observed when the changes are going on incident to the discussion of an absorbing topic, the action being more marked now in this group of muscles and now in that, so that people casually meeting the patient frequently get the impression that there is some mental defect.

"There is no spontaneous movement during sleep or waking repose, but a comparatively slight voluntary movement gives rise to very extensive and peculiar movements in muscles far removed from those required for the execution of the act. For instance, when the patient puts out his hand to take a book from the table beside which he may be sitting, the whole upper part of the body goes through a series of irregular movements highly suggestive of chorea. This is particularly the case with the head, which is somewhat inclined forward, moved from side to side, and the chin is protruded; and there is often an associated movement of the other hand. In none of these movements is there ever anything approaching a jerk.

"*Oculist's Report.*[1] Patient states that for ten years past he has suffered from some gradual impairment of vision and has had double vision at times, of not more than a few days' duration, but not for several years past. Examination shows marked ptosis when the patient is at rest, but by an effort he can raise the lids, showing sclerotic above the cornea when the eyes are directed in a horizontal plane. There is perfect co-ordination of the ocular muscles except to extreme right, where there is slight lagging of the external [lateral] rectus—not enough, however, for the production of diplopia; the lids and conjunctivæ are normal.

"The pupils respond to light but very slowly, and the same is true of accommodation. Dilatation also occurs slowly on stimulation of the skin of the neck.

[1] This case and five others of the series were thoroughly examined by Dr. W. F. Montgomery, Professor of Ophthalmology in the Woman's Medical College, whose reports I herewith append. Two of the less advanced cases (XIX. and XX.) were minutely examined by Dr. Casey Wood, Professor of Ophthalmology in the Postgraduate Medical School in this city.

"Vision is 20/200 in either eye. Snellen No. 5 *can* be read, though with difficulty, at eight inches in an ordinary light; much more easily in a dim light.

"The ophthalmoscope shows a decided blanching of the optic disks and lessening of the caliber of the arteries, with slight but distinct atrophic changes in the retina.

"There are only slight peripheral limitations of the field, and almost complete color-blindness, red only being distinguished with any degree of certainty.

"[Articulation was very much affected, and in view of this fact I am greatly surprised that I did not call attention to it more explicitly in my original publication. By exercising much care and deliberation the patient was easily understood, but even then the labials were often indistinct; with less attention the articulation became somewhat confluent, with considerable elision in polysyllables. Forced utterance was conspicuous, owing, obviously, to inco-ordination between the muscles concerned in respiration, articulation, and phonation, respectively.]

"All the above-described symptoms advanced now more rapidly, now more slowly, up to the time of death, which occurred from simple exhaustion, emaciation having become extreme, and no intercurrent disease having been discovered either by antemortem or postmortem examination. For several days prior to death the patient was unable to utter a sound or move a limb; the only evidence he gave that he heard what was said to him having been afforded by a slight movement of the brows.

"For the last three years he had been unable to see well enough to read, but up to the end he could distinguish outlines of large figures under favoring conditions of light. The articulation had gradually failed, so that for a number of months it had been little more than a succession of grunts, intelligible only to his nurses, and vocal efforts almost invariably provoked paroxysms of coughing with distressing signs of strangulation. For fully a year before the end, and while he still had sufficient strength, he was unable to use table utensils in eating, and, though he could support his weight on his legs, he could make no progress in walking on account of the extreme ataxia, even when assisted, and for more than a year had ceased making the attempt."

Clinical Notes of Case XX.,[1] Brother of Case XVIII., Made in June, 1891.

"Business man, aged twenty-four years, single, well developed, cheerful disposition, and correct habits. General health always good. Did well in his studies at school and excelled in athletic sports. The ataxia appeared without exciting cause at the age of eighteen years. The unsteadiness of gait and some uncertainty in the use of the hands and difficulty of articulation came on together, and not until two years later was any visual defect realized. He has carried a cane for the last few months, but can walk fairly well without one, though deviating considerably from a straight line. He thinks his strength is in no way impaired, for only a few weeks ago he rode a successful tandem race with a brother who is not affected.

"*Examination.* The knee-jerks are markedly exaggerated and all other reflexes active. There is well-marked ataxia in all four extremities. All usual movements, however, can be performed, though with evidently increased deliberation and attention. When in repose the facial muscles are considerably relaxed, giving the patient a heavy and stolid expression, which is often quite at variance with the prevailing state of mind. But during conversation the expression is similar to that already noted in the preceding case.

"*Oculist's Report.* There is marked static ptosis, greater in the left eye, with inco-ordinate overaction of the levator. All movements of the ocular muscles and all pupillary reflexes are sluggish. All are present, however, and in no event can nystagmus be produced. Vision is 20/80 in each eye, and Snellen No. 3 is read well enough at ten inches. Patient reads much better in a dim light. The average expert would pronounce the fundus normal, without knowing anything of the condition of vision. The color-sense is not much affected, and there is some peripheral limitation of the field of vision. All the negations mentioned in connection with the preceding case might be repeated in reference to this one.

[1] Inasmuch as death occurred in this case in a comparatively early stage of the disease, both from my notes and from memory I have expanded and elaborated somewhat the record as first published. At that time it only appeared necessary to identify the case so as to warrant its incorporation into the series. Now it is a question of correlating the anatomic findings with the symptoms.

"The disease had progressed steadily and evenly, but not very rapidly, up to within fourteen months prior to death, which occurred in 1897, when symptoms of pulmonary tuberculosis made their appearance and advanced to a fatal termination. Apart from the weakness incident to the intercurrent disease, the patient was able to walk without assistance, feed and dress himself, read ordinary print, and easily make himself understood in conversation up to the end. The knee-jerks were much more markedly exaggerated and ataxia of all voluntary movements were more pronounced than when the case was first reported. There was at no time any mental defect, diplopia, disorder of general sensation of the special senses, except vision, or the sphincters, nor was there any muscular atrophy or trophic changes.

"If intercurrent disease had not intervened, it appears to me reasonable to assume that in a few years this case would have advanced to a condition of utter helplessness."

Incidentally Case XIX. died from simple exhaustion within the present year, all the symptoms originally enumerated having greatly advanced and no new ones having been added.

A son of Case XVI. has well-marked symptoms of the disease, which first appeared at the age of eighteen years, five years before I examined him last year.

Many thanks are due Dr. R. L. James, of Blue Island, Ill. ; the family of both patients, for reporting to me their condition from time to time, and for assisting at the autopsy in Case XVIII., and to Dr. C. L. Minor, of Asheville, N. C., for holding the autopsy in Case XX.

THE ANATOMIC FINDINGS.

The brain and cord of Case XVIII. were hardened in Müller's fluid and sent in this from Chicago to Baltimore, where this study was begun. The tissues from Case XX. were removed by Dr. Charles L. Minor. The mass of the brain and cord was hardened in formalin, but special pieces of tissue were prepared in a series of fixing reagents at my suggestion. I wish here to express my sincere thanks to Dr. Minor for the care and fidelity with which he followed out all the details of these suggestions.

The tissues of these cases represent material so rarely available that

it has seemed to me desirable to put on record a rather full account of the general morphology of the specimens, so that other investigators, dealing with similar cases and wishing to compare them with these, may find in this article a sufficiently detailed description. For this reason, a description which might otherwise have seemed unnecessarily prolix will be justified.

Description of a More Advanced Case (Case XVIII. of Sanger Brown's Series).

cerebrum of case xviii. hemisphærium dextrum. (Figs. 3, 6, 7 and 11.)

Fissura Sylvii. Distance from ramus anterior horizontalis to ramus posterior ascendens 5.5 cm. The ramus anterior horizontalis is 2 cm. long, reaching to within 0.8 cm. of the sulcus frontalis inferior. The ramus anterior ascendens is rudimentary in reality, though at first sight it would appear to be well marked. On close examination it is seen that what appears to be it is a sulcus which anastomoses above with the sulcus frontalis inferior, and superficially below with the fissure of Sylvius, though it does not cut through the opercular margin. The real ramus ascendens is situated just behind this, and is scarcely visible from the surface. It makes a small incisure only between the pars opercularis and the pars triangularis of the gyrus frontalis inferior.

The fissure of Sylvius bifurcates behind into a ramus posterior ascendens 2.8 cm. long and a ramus posterior descendens 1.2 cm. long. A sulcus subcentralis posterior makes a superficial anastomosis with the fissura Sylvii behind, as does a sulcus subcentralis anterior in front of the central gyrus.

Sulcus Centralis [Rolandi]. The medial extremity stops 0.8 cm. short of the medial margin of the hemisphere, 1 cm. in front of the incisura sulci cinguli. The lateral extremity terminates in an obliquely placed basal piece 1.5 cm. long, which runs parallel to the sulcus subcentralis anterior. In its upper part the sulcus is superficially connected with the pars medialis of the sulcus postcentralis. Otherwise it forms no anastomoses. Relative length, 7 cm.; absolute length, 8.4 cm.; inclination of furrow with fissura longitudinalis cerebri, 72°. Neither genu is well marked.

Sulcus Præcentralis. This is distinctly divided into a pars inferior, a pars superior, and a pars medialis.

Pars Inferior. This forms almost a semicircle with concavity backward. The lower extremity cuts deeply into the pars opercularis of the gyrus frontalis inferior, about midway between the sulcus diagonalis and the sulcus subcentralis anterior, ending 1 cm. from the fissura Sylvii. The upper extremity curves backward into the gyrus centralis anterior, just below the gyrus which connects the gyrus centralis anterior with the gyrus frontalis medius. A deep ramus anterior passes forward and upward into the gyrus frontalis medius. The pars inferior communicates superficially about its middle with the sulcus frontalis inferior, though a deep annectant gyrus separates the two sulci in the depth.

Pars Superior. Its lateral extremity begins in a short sagittal piece, placed just above the gyrus connecting the gyrus centralis anterior with the gyrus frontalis medius. The sulcus extends transversally medialward for 3.2 cm., when it is interrupted by an annectant gyrus extending between the gyrus frontalis superior and the gyrus centralis anterior. At the junction of its upper and middle thirds this pars superior anastomoses with the sulcus frontalis superior in front.

Pars Medialis. A transverse sulcus, 2 cm. long, situated a little anterior to the upper part of the pars superior and parallel to it. It gives off a ramus sagittalis posterior, 2 cm. long, which cuts deep into the gyrus centralis anterior, reaching to within 0.7 cm. of the sulcus centralis. No part of the sulcus præcentralis reaches the medial margin of the hemisphere.

Sulcus Frontalis Inferior. It begins behind in the pars inferior of the sulcus præcentralis, to extend forward for a distance of 2.4 cm., to be interrupted there by a superficial annectant gyrus extending from the pars triangularis of the gyrus frontalis inferior to the gyrus frontalis medius. It anastomoses below with the sulcus in the posterior part of the pars triangularis (false anterior ascending ramus of the Sylvian fissure). At its termination behind the annectant gyrus mentioned it turns upward to anastomose with one of the segments of the sulcus frontalis medius. In front of the annectant gyrus is a transversal sulcus 2 cm. long, the lower part of which bisects the pars triangularis. This is probably to be

regarded as the sulcus radiatus of Eberstaller. Running sagittally forward from its middle and curving around the gyrus between it and the upper extremity of the ramus horizontalis of the Sylvian fissure is a sulcus which ends in front in another obliquely placed transversal sulcus, which is to be regarded as the lateral segment of the sulcus frontomarginalis of Wernicke.

Sulcus Frontalis Superior. It begins behind in a pars superior, 2.8 cm. from the medial margin of the hemisphere. It passes forward for 3.3 cm., where it is crossed almost at right angles by a transversal sulcus connected with the complex of the sulcus frontalis medius. The sulcus here makes a slight jog lateralward and is continued for 2 cm. farther forward, when it turns sharply medialward to end 1.4 cm. from the medial margin of the hemisphere. In front of it, between it and the medial limb of the sulcus frontomarginalis, are two more or less transversally placed compensatory sulci. At the point where it turns medialward the sulcus frontalis superior anastomoses with a transversal sulcus which is one segment of the sulcus frontalis medius.

Sulcus Frontalis Medius. Instead of the typical sagittal sulcus, so frequently met with, this hemisphere shows two transversally placed sulci, a sulcus transversus frontalis posterior and a sulcus transversus frontalis anterior, such as Teuchini and Mingazzini describe. The former anastomoses above with the sulcus frontalis superior and ends below close to the sulcus frontalis inferior; the latter anastomoses above with the sulcus frontalis superior, sends a short anterior sagittal ramus into one of the compensatory sulci in front of the sulcus frontalis superior, and lateralward bifurcates. The superior limb of bifurcation runs backward behind the gyrus frontalis medioinferior to anastomose with the sulcus frontalis inferior, the anterior limb terminating in the gyrus frontalis medius.

Sulcus Cinguli. It is of the "continuous" type, there being no subdivision into pars anterior, pars intermedius, and pars posterior. It begins in front below the genu corporis callosi, the gyrus fornicatus intervening, but it does not reach as far as the "carrefour" of Broca. It runs more or less parallel to the corpus callosum, and leaves everywhere between it and that structure a broad gyrus cinguli. Behind the lobulus paracentralis it curves upward

to the margin of the hemisphere and cuts into the facies convexa for a distance of 1.2 cm. It gives off two deep radial rami into the medial surface of the gyrus frontalis superior ; one, a little behind the level of the sulcus frontomarginalis, reaches the medial margin of the hemisphere and extends for a few mm. upon the facies convexa ; the other, 1.5 cm. in front of the level of the pars superior of the sulcus præcentralis, just reaches the medial margin of the hemisphere.

Sulcus Olfactorius. It is situated entirely upon the orbital surface and presents no unusual features.

Sulci Orbitales. The ramus lateralis and ramus intermedius are two long, deep furrows running nearly parallel to each other throughout almost the entire extent of the orbital surface. The sulcus orbitalis transversus is interrupted by them behind. In front of their anterior extremities is a curved transversal compensatory sulcus situated just at the margin of the orbital surface. The ramus medialis is but feebly developed. The medial part of the sulcus orbitalis transversus is deep.

Accessory Sulci of Lobus Frontalis. 1. *Sulcus Diagonalis Operculi.* 1.8 cm. long ; situated in the pars opercularis of the gyrus frontalis inferior. It forms no anastomoses.

2. *Sulcus Frontomarginalis of Wernicke.* It is entirely separated from segments of the sulcus frontalis medius, and is represented by a Y-shaped sulcus complex, the stem of the Y being directed backward into the gyrus frontalis medius. The medial limb of the Y runs almost transversally toward the medial margin of the hemisphere, and near it undergoes tripartite subdivision. The lateral limb of the Y passes sagittally forward and also divides into three parts, the middle branch cutting into the orbital surface. The most lateral segment of the sulcus has been described along with the sulcus frontalis inferior of the sulcus radiatus.

3. *Sulcus Frontalis Medialis.* This sulcus has two well-marked sagittal segments. The more posterior, 1.7 cm. long, ends anteriorly in a transversal piece 1.5 cm. long. The more anterior segment is 2 cm. in length, and gives off a short medial and a short lateral ramus. In front of it, between it and the sulcus transversus frontalis anterior of the sulcus frontalis medius, is a short compensatory transversal sulcus. The ramus posterior of the pars medialis

of the sulcus præcentralis is almost in a line with the sagittal segment of the sulcus frontalis medius.

4. *Sulcus Rostralis.* A deep, well-marked sulcus running for some distance parallel to the anterior part of the sulcus cinguli. It then turns forward and runs to the medial margin of the hemisphere, to anastomose there with one of the branches of the tripartite subdivisions of the medial segment of the sulcus frontomarginalis. There is no sulcus rostralis inferior. Between the two radiating rami of the sulcus cinguli is a long, deep, sagittal sulcus on the medial surface of the gyrus frontalis superior. It gives off a number of short rami into the substance of the gyrus.

Sulcus Paracentralis. About the middle of the lobus paracentralis a vertical ramus from the sulcus cinguli cuts into the substance for a distance of 1.5 cm. In front of this there is an L-shaped depression and behind it a V-shaped depression in the surface.

Sulcus Interparietalis. 1. *Sulcus Postcentralis.* This sulcus is divided into three segments: (*a*) a pars inferior; (*b*) a pars intermedius; (*c*) a pars superior.

The *pars inferior* is an oblique segment 2.5 cm. long, cutting into the gyrus supramarginalis above, and slightly into the gyrus centralis posterior below. Near its lower extremity it anastomoses with the well-marked sulcus subcentralis posterior of Marchand.

The *pars intermedius*, 3.3 cm. long, runs almost parallel to the sulcus centralis. It is limited below by a gyrus connecting the gyrus supramarginalis with the gyrus centralis posterior. Above, it cuts into the gyrus centralis posterior, and a little above its middle it anastomoses with, or gives rise to, the sulcus interparietalis proprius.

The *pars superior* is curved somewhat like the letter S. Its medial extremity is situated behind the incisura sulci cinguli and reaches to within 0.7 cm. of the margin of the hemisphere. The sulcus is markedly convex forward about its middle. Just below this convexity, a short sagittal sulcus, cutting across the gyrus centralis posterior, connects the pars superior with the upper part of the sulcus centralis.

2. *Sulcus Interparietalis Proprius.* It begins a little above the middle of the pars intermedius of the sulcus postcentralis, and extends in a curve backward and medialward to terminate 0.5 cm.

in front of the anterior limb of the U formed by the sulcus paro·cipitalis. At the junction of its middle and posterior thirds it gives off a ramus medialis which extends to the margin of the hemisphere, and makes an anastomosis with one of the sulci in the præcuneus. This ramus medialis gives off a short sagittal branch which passes forward and accounts for the marked anterior convexity of the middle of the pars superior of the sulcus postcentralis. Below the sulcus interparietalis proprius anastomoses with the sulcus intermedius primus of Jensen and also gives off (*a*) a ramus which runs into the gyrus supramarginalis to end blindly in that gyrus, and (*b*) a ramus which extends into the gyrus angularis, passes through, it running almost parallel to the sulcus intermedius primus, to anastomose with the sulcus temporalis superior.

3. *Sulcus Paroccipitalis of Wilder.* It is entirely separated from the rest of the sulcus interparietalis and forms the usual U around the portion of the fissura parietooccipitalis which cuts into the facies convexa. The medial extremity of the anterior limb of the U reaches to within 0.5 cm. of the margin of the hemisphere. From the latter extremity of this limb a ramus sagittalis anterior is given off, which runs forward for 1.3 cm., "overlapping the posterior extremity of the sulcus interparietalis proprius." The posterior limb of the U bifurcates as it approaches the margin of the hemisphere. It forms no anastomosis with the sulcus occipitalis transversus.

Sulcus Parietalis Superior. This sulcus runs nearly transversally on the facies convexa, being situated between the anterior limb of the U of the sulcus paroccipitalis behind and the ramus medialis of the sulcus interparietalis proprius in front. Its lateral extremity is curved a little forward. Medialward it runs to the margin of the hemisphere and anastomoses with sulci on the surface of the præcuneus.

Sulcus Subparietalis. This sulcus is represented by two segments. The anterior segment anastomoses in front with the sulcus cinguli and behind turns up and anastomoses with a vertical sulcus præcuneus. The posterior segment is shallow and irregular. It is limited behind by a gyrus which connects the posterior part of the præcuneus with the gyrus cinguli.

Sulci Præcunei. The præcuneus presents three sulci—one anterior vertical sulcus and two anteroposterior sulci. The anterior

vertical sulcus anastomoses below with the anterior segment of the sulcus subparietalis; it runs backward and upward to the margin of the hemisphere to form a superficial anastomosis with the ramus medialis of the sulcus interparietalis proprius. The two anteroposterior sulci divide the part of the præcuneus behind the vertical sulcus into three parallel gyri. The uppermost anteroposterior sulcus anastomoses at its anterior extremity with the sulcus parietalis superior, which is continued upon the medial surface of the hemisphere.

Fissura Parietooccipitalis. Distance from medial margin of hemisphere to anastomosis with fissura calcarina, 3 cm.; extent upon facies convexa, 2.2 cm. On the medial surface near its upper part it anastomoses with the upper anteroposterior surface of the præcuneus. This corresponds with an anastomosis with a sulcus on the superficies posterior lobi parietalis of the brother's brain. This brain has been hardened in Müller's fluid, and the fissura cannot be opened so as to permit of the examination of the posterior surface of the parietal lobe.

Fissura Calcarina. Length of truncus, 3.5 cm.; length of fissura propria, 3.3 cm. It anastomoses behind with a sulcus which passes downward, cutting off a portion which otherwise would be a part of the gyrus lingualis between it and the polus occipitalis.

Sulcus Occipitalis Transversus. Above, it begins 4 mm. behind the posterior limb of the sulcus paroccipitalis, but is completely separated from it. It passes transversally downward and a little backward to anastomose with a sulcus running at right angles to it.

Sulci Occipitales Superiores. The surface is marked by slight depressions; there are no definite sulci.

Sulci Occipitales Laterales. There is one lateral sulcus, running from a point just above the polus occipitalis forward and downward to the inferior surface of the hemisphere, there to form the posterolateral limb of the H-shaped sulcus complex. Behind the lower part of the sulcus occipitalis transversus a short sulcus runs backward and downward (almost at right angles to the course of the sulcus occipitalis transversus).

Sulcus Temporalis Superior. It begins in front and a little below the polus temporalis and runs backward. The gyrus tem-

poralis superior is very narrow, averaging less than 1 cm. in thickness. The sulcus curves downward in its posterior part, owing to the ramus posterior descendens of the Sylvian fissure. Behind this region it again runs backward for a distance of 2 cm. and then turns sharply upward, curves a little forward, and ends by anastomosing above with the sulcus interparietalis. In this part of its course the sulcus runs almost parallel to the sulcus intermedius primus of Jensen, and between the two is a transversally placed gyrus, cut off from the anterior portion of the gyrus angularis.

Sulcus Temporalis Medius. The brain has been a long time in Müller's fluid and has become brittle. Portions of the surface in the region of the sulcus temporalis medius have been broken off, and the details with regard to this sulcus are obscured. It appears to run sagittally backward for a distance of about 6 cm. and then to be interrupted. The sulci in the lobulus parietalis inferior are well preserved, as are those in the posterior portion of the temporal lobe. The arrangement is peculiar. Behind the terminal part of the sulcus temporalis superior and below the sulcus interparietalis and in front of the sulcus occipitalis transversus is a large, more or less triangular area of brain surface. Within it is a Y-shaped sulcus complex, the stem of the Y (below) corresponding in all probability to a segment of the sulcus temporalis medius (Eberstaller)—*i. e.*, to Wernicke's sulcus occipitalis anterior. The anterior limb of the Y corresponds to the continuation of the stem and represents the sulcus about the extremity of which the gyrus angularis winds. The posterior limb of the Y is the sulcus about which the lobulus parietalis posterior inferior is situated. Cutting into the middle of the area from above is a short descending ramus from the sulcus paroccipitalis. This appears to be the representative of Eberstaller's sulcus intermedius secundus, as it separates the gyrus angularis in front from the lobulus parietalis posterior inferior behind.

Sulcus Temporalis Inferior. It begins in front 2.4 cm. behind the polus temporalis, is a shallow sulcus, and is interrupted by a gyrus which connects the gyrus temporalis inferior with the gyrus fusiformis. Behind, a segment runs on the inferior surface for a distance of 4 cm.; opposite, about the middle of this segment, is the incisura formerly called the incisura præoccipitalis. It leads into an H-shaped sulcus complex in the lower part of the temporal

lobe. The posterior superior limb of this complex passes upward and anastomoses with a sagittal sulcus which runs forward from the lower end of the sulcus occipitalis transversus to cut deep into the gyrus temporalis medius.

Fissura Collateralis. It begins close behind the fissura rhinica, which is here only a shallow incisure and does not communicate with it. Its greatest convexity medialward corresponds to the insertion of the tip of the gyrus lingualis into the gyrus hippocampi. Around its posterior extremity an annectant gyrus passes from the gyrus lingualis to the gyrus fusiformis. The gyrus lingualis is irregularly grooved by three sulci. The largest begins near the angle of junction of the fissura calcarina with its truncus and runs downward and backward, and then lateralward, to form the posterior inferior limb of the H-shaped sulcus complex referred to at the posterior part of the temporal lobe. Passing out of this sulcus, and at right angles to it, are two shallow sulci which anastomose in front with the posterior part of the fissura collateralis.

hemisphærium sinistrum (Figs. 4, 5, 8, 9 and 10.)

Fissura Cerebri Lateralis [Sylvii]. The ramus anterior ascendens and the ramus anterior horizontalis come off from the main fissure by a common stem 1.4 mm. long. This stem bifurcates, and the ramus anterior horizontalis proper is 1.3 mm. long. The ramus anterior ascendens is 1.6 mm. long. The pars triangularis of the gyrus frontalis inferior is thus diminutive. This appears to be in part due to the very marked development of the sulcus diagonalis which cuts very deeply into the pars opercularis and the lower part of the latter is driven deep into the fossa Sylvii.

Sulcus Centralis. The lateral extremity anastomoses with a very well-marked sulcus subcentralis anterior. The latter is 2 cm. long and makes a superficial anastomosis below with the fissure of Sylvius.

Cutting into the operculum from in front in a direction at right angles to the sulcus subcentralis anterior is a little sulcus which does not appear to have been hitherto described. It is situated just below the insertion of the root of the gyrus frontalis inferior into the gyrus centralis anterior.

The sulcus centralis presents about its middle a knee projecting forward, due to an incisure into the gyrus centralis posterior from the sulcus postcentralis.

A second small knee, due to a similar cause, is seen 1.5 cm. from the medial margin of the hemisphere. The medial extremity of the sulcus reaches just to the medial margin of the hemisphere and does not pass over upon the facies medialis. Inclination of the sulcus centralis to fissura longitudinalis cerebri, 70° ; relative length, 7.7 cm. ; absolute length, 9.7 cm.

Other than that with the sulcus subcentralis anterior the sulcus centralis forms no anastomoses.

Sulcus Præcentralis. This presents for examination three portions : a pars inferior, a pars superior, and a pars medialis.

1. *Pars Inferior.* This forms an X-shaped complex, the anterior superior limb of the X being the ramus anterior of Eberstaller, the posterior inferior limb, a ramus posterior passing beneath the insertion of the root of the gyrus frontalis medius into the gyrus centralis anterior. The other two limbs of the X represent the main direction of the sulcus. The latter is 4 cm. long, the ramus anterior 2 cm. long, and the ramus posterior 1.3 cm. long. The pars inferior anastomoses near its lower part with the sulcus frontalis inferior.

2. *Pars Superior.* It is 2.8 cm. long and "overlaps" the upper part of the pars inferior in the greater part of its extent, being situated behind it and separated from it by a superficial gyrus, a part of the gyrus frontalis medius. Near its upper or medial extremity it gives origin to the sulcus frontalis superior, which passes forward at right angles to it. Its medial extremity is separated from the pars medialis by an annectant gyrus which connects the gyrus frontalis superior with the gyrus centralis anterior.

3. *Pars Medialis.* It consists of an obliquely placed H-shaped sulcus complex, situated between the medial extremity of the pars superior and the medial margin of the hemisphere. The cross-bar of the H is the continuation of the general direction of the sulcus præcentralis. The medial extremity of the posterior side-bar of the H just reaches the medial margin of the hemisphere.

Sulcus Frontalis Inferior. This begins behind in the pars inferior of the sulcus præcentralis and passes forward between the gyrus frontalis medius and the gyrus frontalis inferior. About the

middle of the pars opercularis it anastomoses with a very pronounced sulcus diagonalis operculi. Beyond this point the sulcus curves upward and forward to end in the gyrus frontalis medius. Running out of it near its extremity is a sulcus which winds around the gyrus, projecting upward owing to the ramus anterior horizontalis of the fissura Sylvii. This sulcus passes downward and forward to terminate in a transversal sulcus—the lateral limb of the sulcus frontomarginalis (fm_3). In the gyrus frontalis medius, opposite the ramus anterior horizontalis of the Sylvian fissure, is a short, slightly curved transversal sulcus which probably represents the sulcus radiatus of Eberstaller on this side.

Sulcus Frontalis Superior. It begins near the upper part of the pars superior of the sulcus præcentralis, 3.2 cm. from the medial margin of the hemisphere; it passes forward and undergoes a jog, where it is crossed by a deep transversal sulcus of the gyrus frontalis superior. It is then continued forward and medialward to within 1 cm. of the medial margin, when it suddenly curves around lateralward to terminate very close to the sulcus frontalis medius, but without actually anastomosing with the latter. This deflection of the extremity is apparently due to a deep incisure into the facies convexa from the medial margin just in front of it.

Sulcus Frontalis Medius. This is divided into two segments. The more posterior is situated in the gyrus frontalis medius, in front of the ramus anterior of the pars inferior of the sulcus præcentralis. It is 3 cm. long and runs obliquely from behind and below, forward and upward. It gives off two incisures into the brain tissue in front of it.

The anterior segment is separated from the posterior segment by a gyrus connecting the pars medialis of the gyrus frontalis medius with the pars lateralis. It begins behind in a curved transversal basal piece and extends sagittally forward for a distance of 1.5 cm., when it bifurcates to form the middle and medial segments of the sulcus frontomarginalis (fm_1, fm_2).

Sulcus Cinguli. It begins 0.8 cm. behind the carrefour of Broca. It is nowhere interrupted. Behind it ends in an unusual way, reaching the margin of the hemisphere at a point 2.3 cm. behind the sulcus centralis. It does not pass for more than 2 mm. upon the facies convexa. Intercalated between this incisure sulci

cinguli and the sulcus centralis is the pars superior of the sulcus postcentralis. The sulcus cinguli in its course gives off a number of radiating sulci which pass toward the margin of the hemisphere and into the substance of the gyrus frontalis superior.

Sulcus Olfactorius. This is situated entirely on the orbital surface and presents no peculiarities.

Sulci Orbitales. These are very irregular. The sulcus orbitalis transversus of Weisbach is represented in its medial half by short, obliquely placed segments, entirely separated from one another. In its lateral half it is continued deep and extends almost to the Sylvian margin of the orbital operculum.

The ramus lateralis and ramus intermedius go out from the sulcus orbitalis transversus at the same point. The ramus medialis is short and is independent of the sulcus orbitalis transversus.

Accessory Sulci of the Lobus Frontalis. 1. *Sulcus Diagonalis Operculi.* This is very deep, and its lateral extremity, together with the lower part of the whole pars opercularis of the gyrus frontalis inferior, tends to be sunk into the depth of the fossa Sylvii, and to be partially hidden from view by the overlapping lobus temporalis. The sulcus anastomoses above with the sulcus frontalis inferior.

2. *Sulcus Radiatus. Vide supra.*

3. *Sulcus Frontomarginalis* (*Wernicke*). It consists of three segments—medial, middle, and lateral—of which the last-named is independent of the other two. This lateral segment (fm_1) forms the basal terminal piece of the sulcus which behind is continued with the sulcus frontalis inferior. The medial (fm_3) and middle (fm_2) segments represent the limbs of bifurcation of the sulcus frontalis medius. The medial segment reaches to the medial margin of the hemisphere, and the middle segment extends to within 0.7 cm. of the lateral isolated segment.

4. *Sulcus Frontalis Medialis.* There are no sagittal segments whatever to the sulcus. Instead there are five obliquely transversal segments.

5. *Sulcus Rostralis.* This is well developed. It begins behind in Broca's carrefour and follows a course nearly parallel to the margin of the hemisphere, terminating above at the medial margin, 4 mm. behind the medial limb of the sulcus frontomarginalis.

Below the frontal pole another sulcus, representing in all probability the sulcus frontalis inferior, begins, extending for 2 cm. upon the medial surface of the hemisphere, then turns upon the facies orbitalis and runs obliquely forward and lateralward, to end in the anterior part of that surface.

Sulcus Paracentralis. The lobulus paracentralis presents a U-shaped sulcus. The base of the U and its anterior limb are deep; the posterior limb of the U is very shallow.

Sulcus Interparietalis. 1. *Sulcus Postcentralis.* This consists of three segments—inferior, middle, and superior. The inferior segment is only 1.5 cm. long, and about its middle anastomoses with the sulcus retrocentralis transversus of Eberstaller, behind it.

The middle portion is 4 cm. long and anastomoses near its upper part with the sulcus interparietalis proprius. One and a half cm. above its lower end it gives off a ramus sagittalis anterior which cuts deep into the gyrus centralis posterior, and causes a knee in the sulcus centralis.

The superior or medial segment begins 2 cm. from the medial margin of the hemisphere and extends to the margin between the sulcus centralis and the incisura sulci cinguli. Its lateral extremity curves forward into the gyrus centralis posterior. About its middle it gives off a ramus posterior which acts as a compensatory sulcus for the incisura sulci cinguli on the facies convexa.

2. *Sulcus Interparietalis Proprius.* It begins in the upper part of the middle portion of the sulcus postcentralis, and follows a tortuous course backward and medialward. Behind it forms a superficial anastomosis with the U described by the sulcus paroccipitalis. About midway in its course it gives off a ramus medialis which runs medialward and forward toward the medial part of the sulcus postcentralis. The sulcus intermedius primus of Jensen passes lateralward from it between the gyrus supramarginalis and the gyrus angularis.

3. *Sulcus Paroccipitalis.* This sulcus forms the usual U about the fissura parietooccipitalis of the facies convexa. The anterior limb of the U reaches the medial margin of the hemisphere; the posterior limb of the U does not. The posterior limb of the U, together with a sulcus running lateralward from its junction with the foot of the U, makes the sulcus occipitalis transversus.

Sulcus Parietalis Superior. It anastomoses at the medial margin of the hemisphere with the sulcus præcunei.

Sulcus Subparietalis. This sulcus is separated from the sulcus cinguli in front by a gyrus 1.4 cm. wide connecting the præcuneus with the gyrus cinguli. It curves backward and downward, but is separated behind from the fissura calcarina by a gyrus which connects the præcuneus with the gyrus cinguli.

Sulci Præcunei. A vertical sulcus præcuneus anastomoses at the medial margin with the sulcus parietalis superior. It extends downward upon the medial surface to within 0.8 cm. of the sulcus subparietalis. Turning around its lower extremity between it and the sulcus parietalis is a gyrus arcuatus. This gyrus is bounded in front and behind by two vertical sulci præcunei which anastomose below with the sulcus subparietalis and extend to within about 1 cm. of the medial margin of the hemisphere.

Fissura Parietooccipitalis. Distance from medial margin of hemisphere to anastomosis with fissura calcarina, 3.8 cm. Near the medial margin the fissura undergoes tripartite subdivision, one branch passing forward and running along the medial margin of the præcuneus (corresponding to the sulcus on the posterior surface of the parietal lobe of the brother's brain), a second limb cutting backward for 0.5 cm. into the facies convexa on the anterior surface of the occipital lobe), and the third limb passing transversally upon the facies convexa. There is thus left a pyramidal depression at the margin of the hemisphere at the junction of the occipital and parietal lobes where no brain substance exists.

Fissura Calcarina. Length of truncus, 3.2 cm.; length of fissura propria, 3.7 cm. At a point 1.2 cm. from the margin of the hemisphere the fissura undergoes tripartite subdivision, the upper limb passing into the cuneus, the lower into the gyrus lingualis, and the middle (the continuation of the fissura propria) passing to the medial margin to anastomose there with a sulcus occipitalis lateralis.

Sulci Occipitales Superiores. Behind the sulcus occipitalis transversus and medialward from it is a transversal sulcus, short but deep, which reaches medialward as far as the margin of the hemisphere. A second superior sulcus appears as a "compensatory" sulcus posterior to the lateral extremity of the sulcus occipitalis transversus.

Sulci Occipitales Laterales. There are three shallow occipital sulci on the lateral surface of the occipital lobe.

Sulcus Temporalis Superior. It is interrupted opposite the sulcus subcentralis anterior by a gyrus temporalis mediosuperior and farther back by a second similar gyrus. The gyrus temporalis superior is narrow, being 0.8 to 1 cm. in width.

Sulcus Temporalis Medius. The brain has been injured on this side, so that no satisfactory description of this sulcus is possible.

Sulcus Temporalis Inferior. It begins in front near the polus temporalis and passes backward superficially interrupted, to reach the junction of the inferior with the lateral surface at the so-called incisura præoccipitalis. It then turns upward and backward upon the facies convexa ; a superficial sulcus connects the sulcus temporalis medius with the sulcus temporalis inferior in this region.

Fissura Collateralis. It begins in front, behind the fissura rhinica, and passes backward, being markedly convex medialward. It terminates behind at the junction of the inferior with the convex surface of the hemisphere, about 2 cm. behind the point where the sulcus temporalis inferior passes to the convex surface. The gyrus lingualis presents no typical sagittal sulcus, but instead is irregularly subdivided by two sulci which run across the gyrus at right angles to its longest diameter.

THE CEREBELLUM (CASE XVIII). (Figs. 1, 2 and 25.)

This organ looks normal in size and shape. It was divided into sagittal slabs, and sections from each of these were stained by Weigert's method. A sagittal section in the median plane is illustrated in Fig. 25. The drawing was kindly made for me by my associate, Dr. D. G. Revell. The lingula cerebelli is not well preserved and is schematically illustrated.

The lobulus centralis, though well developed, is not very long in its vertical diameter. It does not enter into the formation of the facies superior cerebelli. There are seven *Randwülste* on its anterior surface and five on its posterior surface.

The monticulus, subdivided into culmen and declive, is well developed. As in the brain of the brother, the lobus intermedius (between the lobus centralis and the first part of the culmen) is

unusually well developed. Compare Figs. 25 and 26 with Stilling's Fig. 122. From the vertical limb of the arbor vitæ there are eight offshoots, corresponding to Stilling's C^1 to C^8 (Stilling's *erste bis dritte Wand*), while from the horizontal limb of the arbor vitæ come off the projections corresponding to Stilling's C^9 to C^{14} (Stilling's *vierte bis sechste Wand*). There would seem to be no marked alteration in the number and character of the *Randwülste* on the different *Wände*, though perhaps the depressions between them are rather shallower than normal. The deep slit between the culmen and the declive is continuous lateralward with the sulcus which separates the pars anterior from the pars posterior of the lobulus quadrangularis. The folium vermis comes off from a terminal offshoot of the horizontal portion of the arbor vitæ, in relation to the lowermost portion of the declive.

The tuber vermis, well developed, is arranged around one principal stem of the arbor vitæ, which bifurcates into two main subdivisions.

The pyramis, as is usual, has a single stem of arbor vitæ which bifurcates near the periphery of the vermis inferior.

The uvula is large and well developed; it seems macroscopically quite normal.

The nodulus is perhaps relatively a little small, but otherwise presents normal appearances.

The hemispheres are well developed; the individual parts show the normal characteristic macroscopic arrangement.

MICROSCOPIC EXAMINATION OF CASE XVIII.

All the tissues were hardened in Müller's fluid, and the microscopic examination has therefore been practically limited to the study of Weigert preparations and carmine specimens.

Medulla Spinalis.

Pars Lumbalis (Fig. 44). *Dimensions:* Anteroposterior diameter, 0.7 cm.; transverse diameter, 0.84 cm.

Radices Anteriores et Posteriores. These are small and contain fewer fibers than normal. The connective tissue of the endoneurium is increased in amount. In the anterior roots a very large

proportion of the fibers are small. The number of large fibers appears to be diminished.

Pia Mater. This is thickened, as in the other case, measuring as much as 0.159 mm. in thickness in places.

Subpial Layer of Neuroglia or So-called "Glial Sheath." Maximum thickness opposite anterior horn, 0.045 mm. ; maximum thickness opposite funiculus lateralis, 0.2 mm. ; average thickness over funiculus posterior near medial line, 0.061 mm. ; average thickness over funiculus posterior near entrance of posterior root, 0.053 mm. ; maximum thickness over Lissauer's fasciculus, 0.133 mm.

Sections Stained with Weigert's Myelin Sheath Stain and with Iron Hematoxylin Stain. The tissue does not stain satisfactorily, owing to imperfect hardening. There is no difficulty, however, in coming to a decision as to the state of the various fasciculi.

The different fasciculi of the funiculi anteriores and of the funiculi laterales present no areas of degeneration. The only alterations noticeable in these preparations are met with in the funiculi posteriores. Here there is tolerably symmetrical degeneration of both funiculi. The lightening corresponds in general to the area designated by Flechsig as the "middle root zone." The degeneration is most marked in the middle of the dorsal funiculus at a level drawn through the substantia gelatinosa of the two sides. It extends dorsalward, but leaves Flechsig's dorsal root zone unaffected, the latter sending a triangular process in between the degenerated area and the posterior median septum on each side. Ventralward the degeneration extends almost to the substantia grisea, but the white matter of the dorsal funiculi nearest the gray matter (corresponding to Flechsig's ventral root zone) is less affected. Though the number of fibers is greatly diminished in the lightened areas, the degeneration is only partial. Nowhere have all the fibers disappeared. The lightening is due to the disappearance of a portion of the medullated fibers and to a corresponding increase in the neuroglia. The distribution of the lesion is well shown in Fig. 44.

The gray matter, as a whole, looks less voluminous than normal; the substantia gelatinosa is less deep than in healthy specimens. A section at the level of T. xii was kindly measured by Prof. H. H. Donaldson, who found the area of the white matter

9.375 cm.^{2} and the area of the gray matter 2.186 cm.^{2}, the ratio being 1:4, 3.

Sections Stained with Van Gieson's Method and with Uranium Carmine. The excessive connective tissue in the anterior and posterior roots and in the pia mater is collagenous, white, fibrous tissue staining intensely in acid fuchsin. In the degenerated area in the funiculus posterior the neuroglia is seen to be diffusely increased and stained of a pink or rose-red color, single yellow myelin sheaths or small groups of myelin sheaths standing out sharply on account of their isolation. There is a tendency to the formation of stripes of neuroglia, radiating dorsomedialward from the dorsomedial surface of the substantia grisea of the cornua posteriores. The blood-vessels are larger in these glia bands, and many of them have unusually distinct fibrous tissue coats which stain in acid fuchsin. The fibers which remain undegenerated in the area in which the neuroglia is increased vary in size. I get the impression, however, that the finer fibers of the area have suffered more than the coarser fibers from the disease process.

The anterior-horn cells appear to be reduced somewhat in number. The methods employed do not permit of any satisfactory description of the internal morphology of these cells. The central canal is obliterated, its place being taken by an irregular aggregation of proliferated ependymal cells.

Pars Thoracalis (Upper Part). (Fig. 43.) The cord has been injured somewhat on removal, but the effects of the injury can be easily distinguished, so that there is no doubt as to the actual changes in the tissues.

Measurements: Anteroposterior diameter, 6 mm.; transverse diameter, 7.5 mm. The pia mater is thickened as in the lumbar region. The subpial neuroglia layer is in general delicate in the pars thoracalis.

Sections Stained with Weigert's Myelin Sheath Stain or with Iron Hematoxylin. The anterior and posterior roots are small and the connective tissue is exaggerated in them, though not so markedly as in the roots of the lumbar nerves.

There are no degenerated areas visible in the funiculi anteriores.

The funiculi laterales present marked alterations. On each side the direct cerebellar tract of Flechsig is almost completely degen-

erated. Only here and there can a fiber of large caliber be made out in the area corresponding to this fasciculus. A good many fine fibers are visible in that portion of the area immediately adjacent to the main part of the pyramidal tract, but these are doubtless themselves fibers of the pyramidal tract which are normally mixed in with the fibers of the direct cerebellar tract. This marked area of degeneration of the direct cerebellar tract is situated, as always, in the dorsolateral portion of the funiculus. The ventrolateral region of the funiculus shows no distinct area of lightening, though the large fibers of that region seem to be less numerous than normal. It is, therefore, probable that the ventrolateral cerebellar tract of Gowers has suffered some, though the chief lesion in the funiculi laterales is undoubtedly an extensive degeneration of the dorsolateral direct cerebellar tract of Flechsig.

The pyramidal tract is not degenerated, nor can I make out any alteration in the fasciculus lateralis proprius.

In the funiculi posteriores there are some partial degenerations tolerably definitely localizable. The partial degeneration assumes approximately the shape of the letter W. The lateral limbs of the W correspond to regions in the funiculi cuneati of the two sides; the medial limbs, to the regions in the fasciculi graciles of the two sides. The degeneration is fairly symmetrical. That in the fasciculus cuneatus of each side occupies a rather broad strip corresponding to about one-third of the width of the fasciculus at its broadest part (opposite the substantia gelatinosa). Dorsalward the strip becomes narrower and ceases at some little distance from the dorsal periphery. Ventralward the degenerated area in the fasciculus cuneatus approaches the median line and fuses with that of the fasciculus gracilis. Though this degeneration passes far ventralward, almost to the substantia grisea, it does not quite reach the latter. Flechsig's ventral root zone remains almost entirely undegenerated. A strip of some breadth intervenes lateralward from the degenerated area between it and the substantia grisea of the dorsal horn.

In the fasciculus gracilis the degenerated strip is narrow, rather fusiform, and more medially than laterally situated. The strip is widest and the degeneration in it most intense about midway between the dorsal periphery and the ventral extremity of the fasciculus.

The degenerated area does not extend dorsalward as far as the posterior surface, but growing gradually less distinct terminates at some distance from this. Ventralward the strip fuses laterally on each side with the degenerated strip in the fasciculus cuneatus.

It will be noticed that the description of this degeneration corresponds very closely in a negative way to Trepinski's description in a positive way of his third fetal system in the thoracic portion of the cord. (See Fig. 290, p. 434, of my book on *The Nervous System.*) It also reminds one forcibly of Flechsig's description of the degeneration in a case of incipient tabes in the upper portion of the thoracic cord, described by him in the *Neurologisches Centralblatt* for 1890.

Lissauer's fasciculi are intact on both sides.

These specimens reveal further important alterations in the white fibers which enter the gray matter of the cord. Thus, while Waldeyer's nucleus of the dorsal horn still stains black and is rich in fine medullated fibers, the nucleus dorsalis on each side is almost entirely devoid of them. There is a marked contrast between the nucleus dorsalis of this case and that of the case to be subsequently described, where many of the fine medullated fibers of Clarke nucleus are still retained. The substantia gelatinosa is still crossed with many radiating bands of fine black fibers, and medullated fibers pass forward toward the anterior horns of gray matter.

Sections Stained with Van Gieson's Method and with Schmaus' Uranium Carmine. Specimens stained by these methods demonstrate very beautifully the proliferation of the neuroglia in the areas of partial degeneration in the dorsal funiculi. In the place of the fibers which have degenerated there are dense masses of rose-pink staining neuroglia. The increase in the neuroglia is much more marked in the fasciculus cuneatus than in the fasciculus gracilis. Here, too, as in the pars lumbalis, there is a tendency to the arrangement of the neuroglia in coarse strands radiating out from the dorsal horns of gray matter. In the areas in which the neuroglia is increased, the bloodvessels are larger and have thicker walls than normal. I get the impression that in the areas of partial degeneration the small fibers have suffered more than the fibers of larger caliber.

The appearance of the degenerated area in the lateral funiculus

corresponding to the direct cerebellar tract is very different from that of the partial degeneration of the dorsal funiculi. While in the latter case one is impressed with the proliferation of the glia and the compression of the fibers, in the former it is the great loss of fibers and the spaces formerly occupied by them which strike one rather than the increase in the glia. There has probably been an increase in the glia substance in the region of the direct cerebellar tract, but it is not in the form of solid masses as in the dorsal funiculi, but instead forms a coarse, much perforated network. It looks as though the fibers had simply been dissolved out, and that the glia and ependymal framework normally present had been swollen or slightly exaggerated in amount. Undoubtedly the process involving the glia here is a wholly different one from that which affects the glia in the dorsal funiculi.

The cells in the nucleus dorsalis have almost entirely disappeared.

Here and there a single cell can be made out, probably corresponding to the isolated large fibers still preserved in the direct cerebellar tract.

Pars Cervicalis (Intumescentia). (Fig. 42.) *Dimensions:* Anteroposterior diameter, 6.5 mm.; transverse diameter, 11 mm.

Sections Stained with Weigert's Myelin Sheath Stain or with Iron Hematoxylin. I can make out no alterations in the funiculi anteriores. In the funiculi laterales the dorsolateral areas (direct cerebellar tract) are very extensively degenerated on both sides, though a few more large fibers are preserved on one side than on the other. The ventrolateral areas (region of Gowers' tracts) do not contain so many large fibers as normally, but there is no marked lightening of this region.

In the funiculi posteriores there are extensive areas of partial degeneration, giving rise to moderate lightening in the ventral half of the fasciculus gracilis and in the ventral and middle portions of the fasciculus cuneatus. The dorsal third of the fasciculus gracilis is entirely free from the degeneration process and the periphery of the fasciculus cuneatus is not involved. Ventralward the area of degeneration of the fasciculus gracilis fuses with that of the fasciculus cuneatus. Close to the posterior commissure and gray matter of the dorsal horn the fibers are better preserved. The degeneration is only partial in the lightened areas and is, perhaps, most intense

in the middle of Burdach's and in the ventral third of Goll's fasciculus. The anterior and posterior white commissures present no noticeable alterations.

Sections Stained with Van Gieson's Method and with Schmaus' Uranium Carmine. The decrease of white fibers of the nerve roots, especially in the radices anteriores, is distinctly visible. There are fewer nerve cells in the anterior horns than normal. The proliferation of glia in the degenerated areas in the funiculi posteriores is pronounced. The region of the direct cerebellar tract in the funiculi laterales stains red and the tissue is not dense ; one sees there a much perforated network with only a few medullated fibers retained.

Medulla Oblongata and Pons Varolii. The small size of the medulla oblongata and pons is evident macroscopically. The length of the pons in the ventral middle line is 2.2 cm., transverse distance between nervi trigemini of two sides 3 cm., maximal thickness 2.5 cm. The depression between the pyramis and the oliva is more marked than usual. The lower part of the medulla has been injured on removal of the brain, so that the nucleus funiculi cuneati and the nucleus funiculi gracilis cannot be examined except in their upper parts ; there, however, they are smaller than normal ; the bulk of the upper part of the nucleus funiculi cuneati is certainly diminished. There is slight thinning of fibers in the stratum interolivare lemnisci and also higher up in the lemniscus medialis. The pyramids are well developed and stain normally. The nuclei arcuati are small. The layer of gray matter of the nucleus olivaris inferior looks thinner than normal and the number of cells present in it somewhat reduced. The fibræ olivocerebellares are less prominent than normal, as are also the fibræ arcuatæ externæ. The corpus restiforme is rather smaller than normal, and shows a thinning of fibers with network-like increase of neuroglia. The nuclei nervi hypoglossi are smaller than normal, and contain correspondingly fewer cells. The nucleus on one side contains fewer cells than that on the other. The tractus solitarii are present, and show no recognizable alterations. The tractus spinalis nervi trigemini looks normal. The lateral region of the formatioreticularis and the nuclei laterales are much less developed than in normal specimens, and the notch dorsal to the olive is deepened as in Menzel's case.

The mass of substantia gelatinosa medial to the tractus spinalis nervi trigemini is small.

In the pons the diminution in size is general, but the various structures appear to be fairly evenly developed in relation to one another. The fasciculi longitudinales pontis and fibræ transversæ pontis look normal and the great nuclei pontis are relatively well represented. The masses of gray matter in the pars dorsalis pontis are not markedly altered in appearance.

The Cerebellum.

1. Sagittal Section in Median Plane. (Fig. 25.) (*a*) *The Arbor Vitæ.*

(1) *Main Vertical Limb.* This medullary stem receives as usual the bands of medullated fibers (laminæ medullares) from the first three *Wände* of the monticulus and part of those from the fourth *Wand.* Part of the fiber bands enter the main vertical limb from in front, part from behind. The main vertical limb descends to form with the horizontal limb the fiber mass of Stilling's corpus trapezoideum.

(2) *Horizontal Limb.* This medullary stem receives as usual the vertical laminæ medullares, corresponding to Stilling's fifth and sixth *Wände* and most of the white fibers from Stilling's fourth *Wand.* It runs forward to enter the corpus trapezoideum from behind. Below it receives the *Markäste* from tuber, pyramis, and uvula.

(3) *Stilling's Corpus Trapezoideum.* In the median plane this is of minimum dimensions. Its configuration and contents, however, correspond to Stilling's descriptions of the normal cerebellum. It receives directly or indirectly the laminæ medullares from all the subdivisions of the vermis superior and inferior.

(*b*) *The Great Anterior Decussation Commissure.* This includes the fibers passing from the left lateral half of the vermis into the right half and *vice versa* at the base of the lingula and of the lobulus centralis, and throughout the whole extent of the main vertical limb of the arbor vitæ. It is Stilling's "*grosse vordere Kreuzungs-Commissur.*"

(*c*) *The Posterior Decussation Commissure.* This includes the fibers which run transversely from one side of the worm to the

other at the posterior end of the horizontal limb of the arbor vitæ, immediately after entrance of the *Markäste* of the declive, folium, and tuber.

(*d*) *The Nucleus of the Roof* (*Nucleus Fastigii*). This nucleus, Stilling's *Dachkern*, is in its normal position in the lower half of the trapezoid mass of white matter behind the lingula and the lobulus centralis. Its dimensions are those ordinarily met.

2. Sagittal Section 1 cm. Lateral from Sagittal Median Plane. The section passes through the ala lobuli centralis, the lobulus quadrangularis, the lobulus semilunaris superior, the lobulus inferior, the lobulus biventer, and the flocculus. The appearance corresponds closely to B. Stilling's vol. iii. (atlas), Plate VIII*b*, Figs. 65 and 66.

The transverse, vertical, and obliquely cut fibers in the central white substance correspond in numbers and position to normal descriptions.

The dentate nucleus (*nucleus dentatus*) (Stilling's corpus dentatum s. ciliare cerebelli) in its more medial part is seen in the section. No trace (except one minute island of cells) of the nucleus globosus or of the nucleus emboliformis is present as the section passes just lateralward from these gray masses. In this section the ellipse formed by the cut section of the dentate nucleus is open in the middle below, and also in its anterior superior region. The typical tortuous appearance of the section of the nucleus is present; this is due to the *Zacken* and *Gegenzacken* of Stilling. The greatest length of the nucleus dentatus in the sagittal direction is 18 mm. The cell bodies in the gray matter of the nucleus dentatus as seen in sections at this level are reduced to almost one-quarter the normal number. Within the nucleus dentatus is a mass of nerve fibers for the most part cut obliquely. But instead of the compact, solid masses of medullated fibers usually seen, the fibers are somewhat thinned and under the loop the Weigert preparation shows lightening; the lightening is tolerably general, though it is most pronounced, perhaps, at the upper part and the posterior part of the intranuclear fiber mass.

In this fiber mass are ten or twelve sections through large blood-vessels visible to the naked eye; these vessels are surrounded by large, clear spaces.

The fibræ semicirculares cerebelli, or Stilling's *halbzirkelförmige Faserzüge*, lying in that part of the central white matter of the cerebellum which is situated between the upper margin of the nucleus dentatus and the bases of the various *Wände* of the lobulus quadrangularis, show no alteration that can be made out in the Weigert sagittal section at this place. Between the fibræ semicirculares and the bases of the *Wände* of the lobulus quadrangularis the *guirlandenförmige Fasern* of Stilling are present, and at the bases of the *Wände* themselves the bundles of fibers cut in cross-section, so characteristic of the normal cerebellum, are to be seen in what appear to be normal numbers.

In this central white matter (corpus medullare) beneath the base of the laminæ medullaris of the posterior part of the lobulus quadrangularis, there is a slightly lightened area in the Weigert section; the lightening may be due to a slight thinning of the fibers in this area.

The white matter of the flocculus is well developed and stains normally, as do the laminæ medullares of the other portions of the inferior surface of the hemisphærium cerebelli. The section passes through a part of the corpus restiforme. A histologic study of the substantia corticalis in sagittal sections at this plane reveals no striking alterations. The molecular layer, layer of ganglion cells, and granular layer show normal relative development.

Description of the Less Advanced Case. Case XX.

Cerebrum.

hemisphærium dextrum. (Figs. 12, 14, 16, 17 and 18.)

Fissura Cerebri Lateralis [Sylvii]. *Truncus.* The polus temporalis does not cover more than the middle half of the pars orbitalis of the gyrus frontalis inferior; it fails to reach anteriorly as far as the sulcus orbitalis transversus by a distance of 0.5 cm.

Fissura Propria. The angle formed with the longest antero-posterior diameter is 13°. The linear distance from the junction with the ramus anterior horizontalis to the junction with the ramus posterior ascendens is 6.2 cm. The ramus posterior ascendens goes off at an angle of 71° and is 2.0 cm. in length. The ramus posterior descendens is 1 cm. in length.

Ramus Anterior Horizontalis and Ramus Anterior Ascendens. These arise by a common stem, the horizontal ramus cutting deep into the gyrus frontalis inferior and reaching to within 0.7 cm. of the sulcus frontalis inferior. It is very prominent on the lateral surface of the cerebrum. The ascending anterior ramus is only 0.5 cm. long. It passes upward and backward from the common stem. It is inconspicuous on the lateral surface, especially in comparison with the sulcus diagonalis operculi.

Sulcus Centralis [Rolandi]. The medial extremity extends beyond the junction of the convex and medial surfaces of the hemisphere, encroaching for a few millimeters upon the medial surface. The genu superior is more marked than the genu inferior. The sulcus turns backward into the paracentral lobule and stands in the typical relation to the extremity of the sulcus cinguli (*cf.* Eberstaller). The lateral extremity of the sulcus is situated 1.5 cm. from the fissure of Sylvius. Between it and the fissure of Sylvius is intercalated an oblique sulcus (the course of which is almost perpendicular to that of the lower third of the sulcus centralis). It is 2.3 cm. in length and is bifurcated at its lower extremity. This is evidently a special case of Eberstaller's *ctr.-Furche* (Retzius' "sulcus subcentralis anterior").

No anastomoses with other sulci. Relative length, 7.8 cm.; absolute length, 10 cm. Inclination of sulcus with fissura longitudinalis cerebri, measured on a line drawn from the point where the sulcus cuts the medial margin to the lower extremity of the sulcus, 66°.

Linear Distance of the Medial End of the Sulcus. From the frontal pole, 120 mm.; from the occipital pole, 95 mm.—that is, as 56:44.

Linear Distance of Lateral End. From frontal pole, 89 mm.; from occipital pole, 112 mm.

Sulcus Præcentralis. 1. *Pars Inferior* (*Sulcus Præcentralis Inferior of Eberstaller*). The pars inferior is superficially continuous with the pars superior, though the two segments are distinctly separated from one another by a gyrus in the depth. The lower extremity of the pars inferior reaches to within 0.9 cm. of the margin of the Sylvian fissure, making a deep incisure in the interval between the sulcus subcentralis anterior and the sulcus diagonalis.

The pars inferior about its middle forms a deep anastomosis with the posterior extremity of the sulcus frontalis inferior. At first sight there would seem to be no ramus anterior of Eberstaller (ramus horizontalis of Cunningham) on this side, but on closer examination and comparison with the opposite hemisphere it is seen that in reality such a ramus exists. It is, however, completely separated from the main sulcus by an annectant gyrus extending between the lateral and medial roots of the gyrus frontalis medius.

2. *Pars Superior* (*Sulcus Præcentralis Superior of Eberstaller*). This pars is a transversally placed foot-piece to the sulcus frontalis superior, with which it forms a deep anastomosis. Its lateral extremity extends backward into the gyrus centralis anterior, posterior from the medial extremity of the pars inferior, and reaches within 0.5 cm. of the sulcus centralis. The superficial anastomosis of the pars superior with the pars inferior is situated 1 cm. above and in front of this lateral extremity. The medial extremity of the pars superior fails (by 0.5 cm.) to reach the medial border of the hemisphere, apparently owing to the very marked development there of a sulcus which is probably to be identified with the sulcus præcentralis medialis of Eberstaller. The latter sends two rami forward, one behind, the other in front of the medial extremity of the sulcus præcentralis superior. The more posterior and lateral ramus is separated from the medial extremity of the sulcus præcentralis superior by a narrow gyrus, only 0.4 mm. in thickness. Passing backward from about the middle of the sulcus præcentralis superior, and cutting deep into the substance of the gyrus centralis anterior for a distance of 1.5 cm. is a well-marked branch (ramus sagittalis posterior of Retzius). This is in almost a direct line with the sulcus frontalis superior, and is probably to be recognized as a part of the latter sulcus, instead of as a part of the sulcus præcentralis. The sulcus complex formed by the sulcus præcentralis superior and the sulcus frontalis superior is an unusually good example of the "cruciform type" which has frequently been described.

3. *Pars Medialis* (*Sulcus Præcentralis Medialis of Eberstaller*). This commences on the medial surface in about the middle of the paracentral lobule as a ramus,[1] which begins 0.7 cm. above the

[1] This ramus may represent a sulcus paracentralis proprius.

sulcus cinguli and extends vertically upward for a distance of 1.3 cm., then turns at an angle of 108° forward and slightly medialward for a distance of 1.4 cm., where it bifurcates on the medial margin of the hemisphere to form two slightly curved terminal prongs. One of these runs forward along the edge of the hemisphere for a distance of 1.1 cm.; the other, lateralward for the same distance, to terminate in the gyrus centralis anterior close behind the medial portion of the sulcus præcentralis superior (*vide supra*).

Sulcus Frontalis Inferior. This sulcus is completely interrupted by a superficial annectant gyrus 0.7 cm. broad, which connects the pars triangularis of the gyrus frontalis inferior with the gyrus frontalis medius. This gyrus evidently corresponds to Eberstaller's *vordere Tiefenwindung*. The posterior part of the sulcus anastomoses behind with the pars inferior of the gyrus præcentralis, extends, tortuous, 1.7 cm. forward and somewhat lateralward, and terminates in a transversal sulcus which cuts above into the gyrus frontalis medius to within 0.4 cm. of the sulcus frontalis medius, and below into the pars triangularis to within 0.8 cm. of the ramus anterior horizontalis of the Sylvian fissure.

The anterior part of the sulcus frontalis inferior begins as an oblique slit 1.7 cm. long, and directed from behind and lateralward (in the pars triangularis) upward and medialward into the gyrus frontalis medius. From a little above the middle of this oblique piece the main sulcus runs forward for a distance of 1 cm., and there gives off a short medial ramus which cuts into the gyrus frontalis medius; it then turns abruptly (angle of 85°) lateralward, to end in the middle of a sagittally placed terminal sulcus, 1.5 cm. in length. The latter is situated almost exactly on the border of the orbital surface. The anterior extremity of this terminal piece lies 0.7 cm. in front of the lateral extremity of the sulcus frontalis marginalis. It seems probable that we have here to deal with a fusion of the anterior portion of the sulcus frontalis inferior with the sulcus radiatus of Eberstaller.

Sulcus Frontalis Superior. The anastomosis of this sulcus with the pars superior of the sulcus præcentralis has already been noted. This occurs at a point 2 cm. distant from the medial margin of the hemisphere. The sulcus is continued back into the gyrus centralis anterior. I agree with Eberstaller that this pro-

lougation (called by Retzius the ramus sagittalis posterior of the sulcus præcentralis) belongs in reality to the sulcus frontalis superior.

The main sulcus follows a tortuous course forward and medialward and terminates in front about 2.5 cm. from the margin of the hemisphere. At about the junction of its posterior and middle thirds it gives off a ramus which cuts lateralward and slightly backward deep into the gyrus frontalis medius. Between this ramus and the sulcus centralis is an isolated gyrus which, at first sight, might be thought to belong to the gyrus frontalis superior, but which must be regarded as a part of the medial portion of the gyrus frontalis medius. The sulcus frontalis superior is nowhere interrupted by annectant gyri, nor does it form anastomoses other than that with the sulcus præcentralis.

Sulcus Frontalis Medius. This is a pronounced sagittal sulcus, almost completely dividing the gyrus frontalis medius into two halves, and so establishing the "four-convolution" type of the frontal lobe in this hemisphere. It begins behind close to the inferior portion of the sulcus præcentralis, as a shallow piece which may, in reality, represent a detached ramus anterior of the inferior præcentral sulcus. One and five-tenths cm. in front of its posterior extremity it is crossed by a transversal sulcus 1.5 cm. long; then becoming very deep it extends 1.5 cm. farther forward and bifurcates into a medial ramus 1 cm. long and a lateral (more sagittal) ramus which extends for a distance of 2 cm. and is then interrupted in the depth by an annectant gyrus connecting the pars medialis with the pars lateralis of the gyrus frontalis medius. In front of this gyrus in the depth, the sulcus makes a deep cut backward and medialward into the pars lateralis of the gyrus frontalis medius, while farther onward it bifurcates to form the two limbs of the sulcus frontomarginalis of Wernicke.

Sulcus Cinguli. This sulcus belongs to Eberstaller's "continuous type."

The pars anterior begins under the front part of the genu corporis callosi, passes forward, then upward, and later backward. It is very shallow in all parts of its course and runs unusually close to the corpus callosum, making a very narrow gyrus fornicatus in front. At its posterior extremity it curves up into the medial sur-

face of the gyrus frontalis superior, to terminate 0.7 cm. from the margin of the hemisphere.

The main course of the pars anterior is, however, continued backward as the pars intermedius, the latter being much more widely separated from the corpus callosum than is the pars anterior. Behind the pars intermedius becomes somewhat irregular and goes over into the pars posterior. The ascending portion of the latter undergoes a Y-shaped bifurcation (*lilienartig gegabelt*). The anterior limb of the Y passes up to the medial margin of the hemisphere and terminates a few millimeters behind the medial extremity of the sulcus centralis. The posterior limb of the Y terminates in the præcuneus without reaching the margin of the hemisphere.

Sulcus Olfactorius. Deep; begins 1 cm. from the medial margin, behind. Bifurcates at posterior extremity. No anastomoses. Length, 4.4 cm. Passes forward and medialward. Reaches medial margin and extends 0.7 cm. upon medial surface.

Sulcus Orbitalis. This is of the H type.

The sulcus orbitalis transversus, ramus lateralis, ramus medialis, and ramus intermedius are all present. The ramus intermedius forms a superficial anastomosis with the ramus lateralis. Running backward from the sulcus orbitalis transversus into the gyrus frontalis inferior is a sagittal ramus. Its course is nearly parallel to that of the medial extremity of the sulcus orbitalis transversus.

Accessory Sulci of the Lobus Frontalis. 1. *Sulcus Diagonalis Operculi.* Very deep; typical direction; extends 2.4 cm. on lateral surface and 1 cm. on inferior surface of pars opercularis. No anastomoses.

2. *Sulcus Radiatus.* Cannot be distinctly made out. If present at all it belongs to the sulcus-complex, composed of that part of the sulcus frontalis inferior which lies along the front part of the base of the pars triangularis and anastomoses farther forward with the lateral segment of the sulcus frontomarginalis of Wernicke.

3. *Sulcus Frontomarginalis of Wernicke.* The lateral portion (fm_1) anastomoses with the anterior extremity of the gyrus frontalis inferior; the middle portion (fm_2) is 1.8 cm. long, is entirely in the facies convexa, and is the lateral limb of bifurcation of the anterior extremity of the sulcus frontalis medius, but the posterior of the two is evidently the continuation of the sulcus frontalis

medialis, the anterior being partially separated by a deep annectant gyrus.

4. *Sulcus Frontalis Medialis and Other Accessory Sulci of the Gyrus Frontalis Superior.* The gyrus frontalis superior is divided into two distinct gyri by a well-developed sulcus frontalis medialis (medial frontal sulcus of Cunningham), a deep sagittal sulcus 4 cm. in length. There are no accessory transversal sulci. The marked development of the sulcus frontalis medialis gives rise to that rare appearance known as the "five-convolution" type of frontal brain.

5. *Sulcus Rostralis.* Very deep and well marked. A far more conspicuous sulcus than the pars anterior of the sulcus cinguli. It begins in the lower part of the sulcus rostralis transversus, and, following a course almost perpendicular to the sulcus cinguli, terminates in the gyrus frontalis superior at a point vertically above the anterior extremity of the corpus callosum. A number of radially directed furrows run out from it into the gyrus frontalis superior toward the margin of the hemisphere.

6. *Sulcus Rostralis Inferior.* Well developed; 3.5 cm. long; deep and continuous. Eberstaller says of this sulcus: "Gut ausgebildet findet sie sich nur an sogenannten windungs, bezw. furchenreichen Gehirnen."

7. *Sulcus Olfactorius Transversus.* Shallow; entirely on medial surface of hemisphere. Anastomoses with the sulcus rostralis inferior.

8. *Sulcus Paracentralis.* See description of sulcus præcentralis medialis.

Sulcus Interparietalis. 1. *Sulcus Postcentralis.* This sulcus is continuous and does not anastomose with the sulcus interparietalis proprius. Its lateral extremity anastomoses with the sulcus subcentralis posterior of Marchand. Its medial extremity turns backward and ends 1 cm. from the medial margin of the hemisphere. The sulcus is deep throughout, there being no annectant gyri in the depth.

2. *Sulcus Interparietalis Proprius.* This begins in an X-shaped sulcus-complex. The lateral posterior limb of the X, which cuts across the gyrus angularis, is separated from the rest of the complex by an annectant gyrus in the depth. The medial posterior limb of the X corresponds to the main course of the sulcus sepa-

rating the lobulus parietalis superior from the lobulus parietalis inferior. The medial anterior limb of the X measures 2 cm. in length, the lateral 1.5 cm. The medial posterior limb (main sulcus) passes backward and slightly medialward for 2 cm., where it bifurcates. The medial limb of bifurcation cuts into the lobulus parietalis superior, the other limb communicating superficially with the posterior part of the sulcus interparietalis (the so-called paroccipital sulcus of Wilder).

3. *Sulcus Paroccipitalis of Wilder.* This forms a U around the fissura parietooccipitalis of the facies convexa. Its anterior extremity begins 3 cm. from the margin of the hemisphere, 0.7 cm. in front of the fissura parietooccipitalis. Its posterior extremity is 1.3 cm. from the margin of the hemisphere, where it appears to anastomose with the sulcus occipitalis transversus, but on examination it is found to be separated from it by an interrupting gyrus which reaches almost to the surface.

Sulcus Parietalis Superior. The sulcus appears as a direct transversal continuation of the sulcus præcunei upon the facies convexa. After an extent of 1.5 cm. it ends in a sagittal cross-piece 1 cm. long. It does not anastomose with the sulcus postcentralis or with the sulcus interparietalis.

Sulcus Subparietalis and Sulcus Præcunei. The former forms a superficial anastomosis with the pars posterior of the sulcus cinguli, passes backward for 2.5 cm., and bifurcates into a posterior and an inferior terminal ramus. A little behind its middle it anastomoses with the sulcus præcunei.

Fissura Parietooccipitalis. Distance from medial margin of hemisphere to point of junction with the truncus of the calcarine fissure, 3.8 cm. The fissure extends 1.5 cm. on the facies convexa and then bifurcates into two short superficial terminal rami. On opening up the fissure from the medial surface the superficies posterior lobi parietalis comes into view. A typical gyrus cunei of Ecker exists. Near the medial border of the surface a deep, tortuous sulcus passes upward and about 1 cm. from the medial margin of the hemisphere reaches the facies medialis ; it then turns sagittally forward through the præcuneus for a distance of 2 cm. and then turns vertically upward 1 cm. behind the sulcus præcunei to terminate near the medial margin of the hemisphere.

The portion of the superficies posterior lateral from the sulcus just described is marked near the bottom of the fissura parieto-occipitalis by a transverse sulcus, above which is a V-shaped sulcus. The lateral limb of this V corresponds to the anterior limb of bifurcation of the fissura parietooccipitalis as seen from the facies convexa. There thus arises a diminutive lobulus parietooccipitalis in the sense of Retzius at the lower end of the fissure. It comes, however, in the domain of the gyrus arcuatus posterior of the lobulus parietalis.

Fissura Calcarina. Length of truncus, 1.8 cm. The fissure extends 3.8 cm. beyond the truncus, terminating behind 0.5 cm. from the margin of the hemisphere, where it undergoes a slight bifurcation.

Sulcus Occipitalis Transversus. It begins 0.5 cm. behind the fissura parietooccipitalis and 1 cm. from the medial margin of the hemisphere. Its lateral extremity anastomoses with the sulcus occipitalis lateralis, giving rise to a stellate sulcus-complex at the junction of the occipital and temporal lobes.

Sulci Occipitales Superiores. There is only one such sulcus. It is situated behind the sulcus occipitalis transversus. Slightly curved, it runs parallel to it from below upward to the margin of the hemisphere, and then turns and runs on the medial surface of the lobus occipitalis, delimiting a peripheral gyrus of the cuneus. Parallel to it, and separating the apical from the middle part of the cuneus on the medial surface, is a second short sulcus.

Sulci Occipitales Laterales. Opposite the polus occipitalis and running parallel to the margin of the hemisphere at a distance of 1 cm. from it, is a sulcus 3 cm. long. Only the medial one-fourth of this is above the level of the fissura calcarina of the medial surface. The rest is opposite the gyrus lingualis. Anastomosing with this sulcus near its upper (medial) extremity is a sulcus 3.3 cm. long. At the junction of its medial and anterior thirds it forms a superficial anastomosis with the sulcus occipitalis transversus, though a deep occipitoparietal annectant gyrus prevents fusion in the depth.

Sulci Temporales Transversi. The sulcus temporalis transversus tertius and the sulcus temporalis transversus primus are well marked, but, as the gyrus temporalis transversus primus and the gyrus temporalis transversus secundus are fused, the sulcus temporalis transversus secundus is absent. Opposite the area of fusion there is a sulcus on the external surface of the gyrus temporalis supe-

rior which passes downward on the inferior surface of the gyrus and subdivides this as far as the bottom of the sulcus temporalis superior.

Sulcus Temporalis Superior. The sulcus is very deep and presents transverse gyri on both its walls. Its anterior extremity stops short of the frontal pole. It is not bifurcated, nor is there any transversal sulcus in front of it. At the point where the sulcus turns upward behind it is interrupted by a superficial annectant gyrus temporalis mediosuperior. Behind this the sulcus passes upward and a little backward into the gyrus angularis to within 1 cm. of the sulcus interparietalis. The sulcus intermedius primus between the gyrus angularis and the gyrus supramarginalis makes a superficial anastomosis below with the anterior part of the sulcus temporalis superior. The anterior portion of the gyrus angularis is cut across by a sulcus which anastomoses above with the sulcus interparietalis, below with the sulcus temporalis superior. An oblique sulcus, parallel to the ramus posterior ascendens and the ramus posterior descendens of the fissure of Sylvius, divides the gyrus supramarginalis into a medial and a lateral half. This sulcus anastomoses behind with the sulcus intermedius primus of Jensen.

Sulcus Temporalis Medius. It begins in a slight bifurcation 1 cm. behind the polus temporalis and extends backward 3.8 cm., where it is interrupted by a superficial annectant gyrus temporalis medioinferior. Behind this gyrus it begins again in a basal cross-piece nearly 3 cm. long, which cuts almost through the gyrus temporalis superior; less deeply into the gyrus temporalis medius. It then passes backward to the notch on the margin of the hemisphere formerly called the incisura præoccipitalis, and turns upward and backward for a distance of 4 cm., terminating in an H-shaped sulcus complex in the gyrus parietalis inferior posterior. Between its posterior extremity and the posterior extremity of the sulcus frontalis superior, passing down from the sulcus interparietalis between the gyrus angularis and the gyrus parietalis posterior inferior, is a well-marked sulcus intermedius secundus.

Sulcus Temporalis Inferior. The main portion of this sulcus begins about 2 cm. below and behind the polus temporalis and passes in a curved direction (concavity medialward) backward, to end in a cross-piece 2 cm. long. In front of it, between it and the anterior extremity of the lobus temporalis, is a curved transversal "compen-

satory" sulcus 1.5 cm. long. Running forward to the margin of the poles from near the middle of this is a sagittal ramus 0.8 cm. in length. Behind, the sulcus is represented by a short furrow passing backward for less than 0.2 cm. behind the medial extremity of the so-called incisura præoccipitalis. The gyrus between this and the sulcus occipitalis lateralis is accordingly assumed to be the continuation backward of the gyrus temporalis inferior.

A transverse sulcus connects the fissura rhinica with the sulcus temporalis inferior and separates the incurved extremity of the gyrus temporalis inferior (in front) from the anterior extremity of the gyrus fusiformis (behind).

Fissura Collateralis. Its anterior extremity is separated from the fissura rhinica by a broad gyrus rhinencephalofusiformis. The sulcus is deep and overhung by the gyrus fusiformis. It passes backward in a marked curve with convexity medialward. It anastomoses behind with the sulcus sagittalis gyri lingualis which bisects the gyrus lingualis. The inferior margin of the gyrus lingualis is delimited by part of an H-shaped sulcus complex. The anterior superior limb of this H runs forward into the gyrus fusiformis and subdivides its posterior portion into two sagittal gyri. The more medial of these connects with the inferior portion of the gyrus lingualis, thus forming a gyrus fusiformolingualis. Lateralward from the H-shaped sulcus complex the gyrus lingualis is connected with the gyrus temporalis inferior by a gyrus temporolingualis. The fissura collateralis is separated from the truncus of the fissura calcarina by a broad gyrus rhinencephalolingualis.

Sulci Insulæ. The sulcus centralis insulæ of Guldberg divides the insula into lobulus insulæ anterior and the lobulus insulæ posterior. The gyrus centralis posterior primus, gyrus centralis posterior secundus of the posterior lobulus are fused into a single mass, showing three short superficial sulci on the surface. The lobulus anterior insulæ is divided into four radiating gyri by means of three rather shallow sulci.

hemisphærium sinistrum. (Figs. 13, 15, 16, 17 and 19.)

Fissura Cerebri Lateralis [Sylvii]. *Truncus.* The polus temporalis does not project beyond the pars orbitalis of the gyrus frontalis inferior, except at its posterior border; the extremity

of the polus is more than 1 cm. distant from the sulcus transversus.

Fissura Propria. This forms an angle of 13° with the longest anteroposterior diameter of the hemisphere. The distance from the ramus anterior horizontalis to the ramus posterior ascendens is 7.2 cm. The ramus posterior ascendens goes off at an angle of 68° and is 1.8 cm. long. The ramus posterior descendens measures 1.6 cm. in length. There appears to be only one anterior sulcus, the ramus anterior ascendens, but on close examination a rudimentary ramus anterior horizontalis indicating the limits of the pars triangularis can be made out, cutting only a few millimeters into the cerebral substance.

Sulcus Centralis [Rolandi]. The medial extremity fails to reach by 0.5 cm. the junction of the facies convexa with the facies medialis, notwithstanding the fact that the sulcus cinguli cuts into the facies convexa for a distance of 1.2 cm. The lateral extremity is continuous with the sulcus subcentralis anterior, though there is a low annectant gyrus in the depth separating the two. The anterior subcentral sulcus appears to connect the sulcus centralis with the Sylvian fissure, but on pulling aside the margin of the latter it is seen that the subcentral sulcus terminates in the substance of the inferior surface of the operculum. The genu inferior and the genu superior are both well marked. Relative length of sulcus centralis, 6.7 cm.; absolute length of sulcus centralis, 8.6 cm.; inclination (measured according to Eberstaller),[1] 63°; distance in a straight line of the medial end of the sulcus from the frontal pole, 114 mm.; distance in a straight line of the medial end of the sulcus from the occipital pole, 83 mm.; distance in a straight line of the lateral end from the frontal pole, 93 mm.; distance in a straight line of the lateral end from the occipital pole, 112 mm.

Sulcus Præcentralis. 1. *Pars Inferior* (*Sulcus Præcentralis Inferior of Eberstaller*). This is only superficially connected with the pars superior, an annectant gyrus passing from the medial portion of the base of the gyrus frontalis medius to the gyrus centralis anterior, being depressed below the surface by a shallow sulcus only. The lateral extremity of the sulcus is 0.8 mm. from the margin of

[1] The deformation of the hemisphere in hardening makes this measurement of doubtful value.

the Sylvian fissure, there being no separating sulcus diagonalis on this side. The medial extremity passes in front of the lateral extremity of the pars superior. There is a typical anterior sagittal ramus (ramus horizontalis of Cunningham) passing forward and a little medialward into the substance of the gyrus frontalis medius and terminating in a transversal sulcus 0.8 mm. long. The lateral portion of the foot of the gyrus frontalis medius is connected with the foot of the gyrus frontalis inferior by an annectant gyrus 0.4 cm. in thickness. The latter prevents the anastomosis of the sulcus frontalis inferior with the sulcus præcentralis inferior. The posterior extremity of the sulcus frontalis inferior almost bisects the angle formed by the sulcus præcentralis inferior with its ramus sagittalis inferior.

2. *Pars Superior* (*Sulcus Præcentralis Superior of Eberstaller*). This is an irregular sulcus 3 cm. in length. Its lateral extremity has a shallow sagittal base 1 cm. in length. Its medial extremity passes medialward and a little forward, and, shortly before terminating, bends sharply backward into the gyrus centralis anterior to and 1 cm. from the medial margin of the hemisphere. The sulcus frontalis superior is continuous with the medial extremity of this sulcus. One and one-half cm. lateralward from this anastomosis a ramus sagittalis posterior passes backward into the gyrus centralis anterior, causing a deflection of that gyrus and giving rise to a knee in the sulcus centralis.

3. *Pars Medialis* (*Sulcus Præcentralis Medialis of Eberstaller*). This is represented by a short sulcus in the gyrus centralis anterior between the medial extremity of the pars superior of the sulcus præcentralis and the sulcus centralis. Its medial extremity begins 2 mm. from the medial margin. The sulcus has a transversal limb extending directly lateralward for a distance of 1.5 cm. It then turns at a right angle and runs sagittally backward for 1 cm. to terminate within 0.4 cm. of the pars superior.

Sulcus Frontalis Inferior. The sulcus is continuous superficially. It is prevented from uniting with the pars inferior of the sulcus præcentralis by a superficial annectant gyrus extending between the pars opercularis of the gyrus frontalis inferior and the lateral portion of the foot of the gyrus frontalis medius. It begins behind, close to the angle formed by the pars superior of the sulcus

præcentralis with its ramus sagittalis anterior, passes forward and a little lateralward for a distance of 3.5 cm., and ends in the middle of an obliquely transverse terminal sulcus 3 cm. long. The medial limb of this terminal cross-piece cuts into the gyrus frontalis medius to within 0.7 cm. of the sulcus frontalis medius, while the lateral limb cuts into the pars triangularis to within 0.5 cm. of the rudimentary ramus ascendens horizontalis of the fissure of Sylvius. Cutting into the gyrus frontalis medialis from about the middle of the sagittal portion of the sulcus frontalis inferior is a short medially directed ramus. Eberstaller's *vordere Tiefenwindung* is distinctly visible in the depth in front of the latter.

Sulcus Frontalis Superior. The sulcus anastomoses behind with the upper part of the pars superior of the sulcus præcentralis, though they are partially separated by a deep annectant gyrus. The sulcus at its posterior extremity is only 1.5 cm. from the medial margin of the hemisphere. It is not prolonged behind the sulcus præcentralis into the gyrus centralis anterior. It passes forward and a little lateralward (instead of as usual medialward) and forms in front a superficial anastomosis with the sulcus frontalis medius, an annectant gyrus making the communication a very shallow one. The sulcus is not interrupted. It presents incisures into the gyrus frontalis superior above and the gyrus frontalis medius below. In front of the anastomosis with the sulcus frontalis medius is a short, isolated, obliquely sagittal sulcus, and in front of this again a transversal sulcus 2.5 cm. long on the facies convexa, and extending for 1 cm. upon the facies medialis. These two isolated sulci, although behind the sulcus frontomarginalis, may, perhaps, be regarded as interrupted segments of the anterior extremity of the sulcus frontalis superior.

Sulcus Frontalis Medius. The sulcus on this side is very irregular. One cm. in front of the anterior termination of the ramus anterior of the inferior portion of the sulcus præcentralis is a transversal sulcus 3 cm. long, shallow, and unconnected with other sulci. One and one-half cm. farther forward the sulcus frontalis medius proper begins as a transversal basal piece. The medial extremity of this forms a superficial anastomosis with the sulcus frontalis superior. Passing forward from the middle of this basal sulcus a sagittal sulcus extends 1.5 cm. forward, and then

bifurcates into the two limbs of the sulcus frontomarginalis of Wernicke.

Sulcus Cinguli. It consists of two pieces, the pars posterior and the pars intermedius being continuous, the pars anterior being separated from the rest of the sulcus. The pars anterior begins in its usual position between the genu corporis callosi and extends forward and then upward, cutting through the medial surface of the frontal lobe to reach the margin of the hemisphere about 4 cm. behind the frontal lobe. The pars intermedius commences about 1 cm. in front of the anterior extremity of the corpus callosum and in the plane of the superior surface of that structure. It curves backward approximately parallel to the corpus callosum, and, becoming continuous with the deep pars posterior, passes up behind the lobulus paracentralis to the margin of the hemisphere, and even extends for a distance of 1.3 cm. upon the convex surface.

Sulcus Olfactorius. One cm. deep, 4.4 cm. long. It passes forward and slightly medialward, but fails to reach the medial margin by 0.4 cm. No anastomoses.

Sulcus Orbitalis. It is much more irregular than on the right side. The sulcus orbitalis transversus is marked and anastomoses with the ramus lateralis and ramus intermedius. The ramus medialis is shallow and does not communicate with the sulcus orbitalis transversus, nor with the ramus intermedius.

Accessory Sulci of the Lobus Frontalis. 1. *Sulcus Diagonalis Operculi.* Absent on this side, or possibly represented by the lower part of the sulcus præcentralis inferior.

2. *Sulcus Radiatus.* Not represented, though some might look upon the transversal termination of the sulcus frontalis inferior as representing the sulcus radiatus.

3. *Sulcus Frontomarginalis* (*Wernicke*). The lateral segment (fm_1) is absent. The middle and medial segments (fm_2, fm_3) are present and appear as limbs of bifurcation of the anterior extremity of the sulcus frontalis medius. The medial limb is directly continuous in the depth with the sulcus frontalis medius, but the middle portion is partially separated by a deep annectant gyrus. In front of fm_2, fm_3 is a transverse sulcus situated exactly on the orbital margin. It may be regarded as a doubling of fm_3.

4. *Sulcus Frontalis Medialis and Other Accessory Sulci of the Gyrus Frontalis Superior.* There is no continuous sagittal sulcus on this side. In the posterior part of the gyrus frontalis superior is an oblique curve. Farther forward are two transversal curves cutting almost entirely across the gyrus. Still more anteriorly is an oblique curve 2.5 cm. long, passing from behind and near the medial margin forward and lateralward. About half-way between this and the medial limb of the sulcus frontomarginalis is a transversal sulcus extending 2.5 cm. upon the facies convexa and 1 cm. upon the facies medialis. The medial surface of the gyrus frontalis superior, aside from the sulci rostrales, is unusually deeply and multiply fissured.

5. *Sulcus Rostralis.* Deep and well marked; begins below the knee of the corpus callosum, runs parallel to the pars anterior of the sulcus cinguli, and terminates in a Y-shaped bifurcation. The posterior limb of the Y anastomoses with a short ramus given off by the pars anterior sulci cinguli near its extremity.

6. *Sulcus Rostralis Inferior.* Three cm. long, deep; well marked.

7. *Sulcus Olfactorius Transversus.* Well developed; 1.5 cm. long; situated entirely on the facies orbitalis.

Sulcus Paracentralis. Above the pars posterior of the sulcus cinguli is a sulcus 3.5 cm. long dividing the lobulus paracentralis into an upper and lower portion. At the anterior extremity of this sulcus a vertical ramus passes up to the margin of the hemisphere and extends for a distance of 0.4 mm. upon the facies convexa. The posterior extremity of the sulcus paracentralis is bifurcated.

Sulcus Interparietalis. 1. *Sulcus Postcentralis.* The sulcus is subdivided into a shorter superior and a longer inferior portion. The pars superior begins on the medial margin of the hemisphere, curves lateralward, and then forward around the incisura sulci cinguli, and terminates close to the sulcus centralis. The pars inferior is an obliquely transversal sulcus, 2.5 cm. long, bifurcated at both extremities. It forms no anastomoses. It is separated from the pars superior by a gyrus which connects the gyrus centralis posterior with the lobulus parietalis superior. It is separated from a deep sulcus subcentralis posterior by a gyrus which connects the gyrus centralis posterior with the lobulus parietalis inferior.

2. *Sulcus Interparietalis Proprius.* It begins 0.7 cm. behind the sulcus postcentralis inferior, being separated from it by a gyrus connecting the lobulus parietalis superior with the lobulus parietalis inferior. It passes obliquely backward and medialward to anastomose with the sulcus paroccipitalis behind and with the sulcus parietalis superior medially. In the depth it is partly separated from each by annectant gyri.

3. *Sulcus Paroccipitalis of Wilder.* The sulcus forms a U embracing the portion of the fissura parietooccipitalis which cuts into the facies convexa. The posterior limb of the U, after giving off a short lateral ramus, passes medialward and backward almost to the edge of the hemisphere. It does not anastomose with the sulcus occipitalis transversus.

Sulcus Parietalis Superior. An S-shaped sulcus on the facies convexa situated between the pars superior of the sulcus præcentralis in front and the fissura parietooccipitalis behind. Its medial extremity begins at the medial margin of the hemisphere just in front of the sulcus præcunei, being separated from the latter by an annectant gyrus. Its lateral extremity forms a superficial anastomosis with the sulcus interparietalis proprius. There is a shallow, short, oblique groove in the cortex between the sulcus præcentralis superior and the sulcus parietalis superior (in the gyrus arcuatus medius), and a second shallow groove between the sulcus parietalis superior and the fissura parietooccipitalis (in the gyrus arcuatus posterior).

Sulcus Subparietalis. Its anterior extremity is separated from the sulcus cinguli by a gyrus connecting the gyrus fornicatus with the præcuneus. Its posterior extremity is separated from the truncus of the fissura calcarina by a gyrus 1 cm. broad connecting the posterior inferior angle of the præcuneus with the gyrus cinguli.

Sulcus Præcunei. A deep sulcus, running upward and backward from the middle of the sulcus subparietalis, bisects the præcuneus; its upper extremity terminates on the medial margin of the hemisphere just behind the beginning of the sulcus parietalis superior. The anterior and posterior halves of the præcuneus are in turn bisected by irregular vertical sulci which anastomose below with the sulcus subparietalis, terminating above in the substance of

the præcuneus short of the margin of the hemisphere. The anterior vertical ramus is bifurcated at its upper extremity.

Fissura Parietooccipitalis. Distance from the medial margin of the hemisphere to point of junction with the truncus fissuræ calcarinæ, 4 cm. The fissure extends 1.7 cm. upon the facies convexa and ends without bifurcation. A typical gyrus cunei of Ecker exists. The superficies posterior lobi parietalis is very simple. There is a marked gyrus cuneoprælunatus at about the junction of the lower and middle thirds. Above this the surface is concave and slightly irregular. There is no lobulus parietooccipitalis.

Fissura Calcarina. Length of truncus, 1.9 cm. Length of fissura propria, 3.8 cm. The fissura is separated from the fissura parietooccipitalis in the depth by an annectant gyrus which extends from the cuneus to the gyrus cinguli. The fissura propria follows a sinuous course to the margin of the hemisphere and extends for a distance of 1.2 cm. upon the facies convexa. A sulcus sagittalis inferior cunei (Retzius) passes through the lower part of the cuneus running approximately parallel to the fissura calcarina. It extends also for a distance of 1.1 cm. upon the facies convexa.

Sulcus Occipitalis Transversus. This is a deep sulcus, entirely separated above from the end of the sulcus paroccipitalis by an annectant parietooccipital gyrus 0.6 cm. broad. The course of the sulcus is sinuous. It is very convex forward below its middle. Length, 4 cm. It ends below about 1 cm. above the lower margin of the facies convexa. It forms the two posterior limbs of an X-shaped sulcus complex situated at the posterior extremity of the lobus parietalis.

Sulci Occipitales Superiores. There is only one such sulcus. It is 2 cm. long, begins 0.5 cm. below the posterior curve of the sulcus paroccipitalis, runs nearly parallel to the upper part of the sulcus occipitalis transversus, and terminates 0.4 cm. above the uppermost sulcus occipitalis lateralis. About its middle it gives off a posterior ramus less than 0.5 cm. long.

Sulci Occipitales Laterales. Of these there are two connected by a cross-piece and giving rise to an H-shaped sulcus complex. The upper of these begins 0.6 cm. behind the sulcus occipitalis transversus, and ends behind near the margin of the hemisphere

about midway between the sulcus sagittalis cunei and the fissura calcarina. The lower one ends behind below the fissura calcarina on the facies convexa, close to the polus occipitalis.

Sulci Temporales Transversi of Heschl. The sulcus temporalis transversus tertius separates the gyrus temporalis transversus secundus from the gyrus temporalis transversus tertius ; it is a deep, well-marked groove which reaches the free surface of the gyrus temporalis superior and cuts through it into the sulcus temporalis superior, just in front of a well-marked superficial gyrus temporalis mediosuperior secundus which exists on this side. The sulcus temporalis transversus secundus is marked only in its posterior part. The sulcus temporalis transversus primus is a very shallow groove separating the gyrus temporalis transversus primus from the insular portion of the surface.

Sulcus Temporalis Superior. It begins behind the polus temporalis, an obliquely placed "compensatory" sulcus intervening. One centimeter behind its anterior extremity a sulcus goes off from it backward and downward to the sulcus temporalis medius. The sulcus temporalis superior is continued backward to about the junction of its anterior and middle thirds, where it is interrupted by a superficial gyrus temporalis mediosuperior secundus. Behind this gyrus the sulcus begins again in the middle of a long, curved, transversal sulcus, the extremities of which cut into the gyrus temporalis superior and the gyrus temporalis medius, respectively. The sulcus itself passes backward, curves around the projection of the gyrus temporalis superior, caused by the ramus posterior descendens of the Sylvian fissure, and then turns upward to end 0.6 cm. from the sulcus interparietalis, midway between the sulcus intermedius primus and the sulcus intermedius secundus of Jensen. At the point where the sulcus temporalis superior turns upward it anastomoses freely with the sulcus which runs backward into the lobulus parietalis posterior inferior and communicates behind with the anterior superior limb of the X-shaped sulcus complex mentioned in connection with the sulcus occipitalis transversus.

Sulcus Temporalis Medius. It is manifoldly interrupted. It begins as a curved, obliquely-placed sulcus, 2 cm. long, situated in front of the anterior extremity of the sulcus temporalis inferior, the segment looking like a "compensatory" sulcus for the latter. A

little farther back is a shallow, curved sulcus, 1.5 cm. long, connected with the oblique sulcus which anastomoses with the anterior portion of the sulcus temporalis superior. Farther back are two long, curved depressions, both of which cut deep into the gyrus temporalis medius, the anterior one cutting deep into the gyrus temporalis inferior. The posterior extremity of the more posterior of the two anastomoses with the transversal sulcus, which, in turn, forms a superior superficial anastomosis with the sulcus temporalis inferior. A broad gyrus temporalis medioinferior now interrupts the sulcus, which begins again behind it as an obliquely transversal furrow, from the middle of which the sagittal sulcus passes backward and then curves upward and backward to run toward the lobulus parietalis posterior inferior. The sulcus just above this, terminating in the lobulus parietalis posterior inferior, may be considered, if desired, as the most posterior segment of this sulcus temporalis medius.

Sulcus Temporalis Inferior. It begins 2 cm. behind the polus temporalis and runs backward for 5.5 cm. It is then interrupted by a gyrus connecting the gyrus temporalis inferior with the gyrus fusiformis. Behind this annectant gyrus a sagittal continuation of the sulcus forms the cross-piece of the H-shaped sulcus complex, the side bars of the H being transversal sulci which pass down from the sulcus temporalis medius, across the gyrus temporalis inferior into the gyrus fusiformis. Another annectant gyrus between the gyrus temporalis inferior and the gyrus fusiformis again interrupts the sulcus. Behind this the continuation of the sulcus forms the top piece to a π-shaped terminal sulcus complex. Between its posterior extremity and the lower extremity of the sulcus occipitalis transversus a third gyrus connects the gyrus temporalis inferior with the gyrus fusiformis.

Fissura Collateralis. This is shallower than on the right side, is separated in front from the gyrus hippocampi by a long, narrow gyrus which runs from the incurved polus temporalis to the middle of the gyrus hippocampi. Behind, it ends near the posterior extremity of the hemisphere, in an oblique transversal cross-piece, the medial limb of which goes between the two vertical pieces of the π-shaped sulcus complex at the posterior extremity of the sulcus temporalis inferior. The gyrus lingualis is subdivided by

a sagittal sulcus which anastomoses in front with the fissura collateralis below the annectant gyrus rhinencephalolingualis.

Sulci Insulæ. Guldberg's central sulcus of the island separates the posterior lobe with its two gyri from the anterior lobe with its four gyri.

THE CEREBELLUM. (Figs. 21, 22, 23, 24 and 26.)

The cerebellum looks a little small. It has, however, been distorted in the hardening process. The actual measurements are as follows: Length (anteroposterior), in the middle, 4.1 cm.; right side (maximal), 6.7 cm.; left side (maximal), 6.6 cm.; greatest transverse diameter, 9.2 cm.; greatest height or thickness, 4.2 cm. The distortion has flattened the vertical and increased the anteroposterior diameter. The incisura cerebelli posterior is deep.

Vermis. The lingula cerebelli has been torn in separating the cerebellum from the rest of the brain stem. It is well developed, is not atrophic or rudimentary, and is a lingula simplex, not duplex. The vincula lingulæ cerebelli are symmetrical and not separated from the lingula by notches. The two sides of the posterior free surface of the lingula are symmetrical. The anterior surface is firmly fused posteriorly with the velum medullare anterius.

Lobulus Centralis. This is well developed. It lies almost entirely on the anterior free surface of the cerebellum, but its most superior portion is visible from the facies superior, and thus enters to a slight extent into the formation of this surface. On its anterior surface eight *Randwülste* are present, separated from one another by depressions. These *Randwülste* run in general parallel to one another and vary only slightly in thickness. The upper three *Randwülste* are marked off from the ala lobuli centralis on each side by deep indentations; below these three, however, the junction is grooved, but there is no incisure. The delimitation is more sharply marked off on the left than on the right side.

The posterior surface of the lobulus centralis is slightly concave. It presents seven *Randwülste* of approximately equal width. There are no incisures between the *Randwülste* of the central lobule and its alæ.

The apex of the central lobule is rather blunt.

The dimensions of the lobulus centralis are as follows: A. Of

facies anterior: 1. From above downward (apex to base)—in the middle, 17 mm. (Stilling's normal measurements vary between 10 and 20 mm.) 2. From right to left: Above, 9 mm. (Stilling's normal, 4–10 mm.) Middle, 9.5 mm. (Stilling's normal, 6–10 mm.) B. Thickness: Just beneath apex, 2 mm.; in the middle, 5 mm.; at the base, 4 mm.

The alæ lobuli centralis present on both sides the typical double concavity on the anterior free surface corresponding to the brachium conjunctivum and the brachium pontis. The anterior free surface of each ala is subdivided by sulci into numerous *Randwülste* more markedly than in most of Stilling's cases; the configuration is somewhat different on the two sides. The right ala presents seven *Randwülste*, the longest being the fifth, which measures 15 mm.; the upper two are the shortest. The sulci do not extend all the way to the posterolateral margin. There is no fusion with the brachium conjunctivum, the two being separated by the pia mater. The left ala also presents seven *Randwülste*. There is a tendency to a radial arrangement of the sulci from a center situated near the lateral apex. An area which is not subdivided exists near this apex. The posterior free surface of the alæ presents well-marked *Randwülste* and sulci; on the left side this surface is fused with the lobus intermedius. The dimensions of the anterior surface of the alæ lobuli centralis are as follows:

From above downward: (*a*) Next the lobulus centralis, right side, 12 mm.; left side, 11 mm. (Stilling's average, 11–12 mm.) (*b*) In the middle, right side, 10 mm.; left side, 10 mm. (Stilling's average, 7–8 mm.) (*c*) Behind middle of brachium pontis, right side, 7 mm.; left side, 10 mm. (Stilling's average, 4–5 mm.) Width: (*a*) Upper margin, right side, 18 mm.; left side, 22 mm. (Stilling's average, 16–22 mm.) (*b*) Lower margin, right side, 16 mm.; left side, 18 mm. (Stilling's average, 14–20 mm.)

In general, then, it may be stated that the lobulus centralis and its alæ are well developed and the asymmetry is within normal limits.

Monticulus. The monticulus on examination is found to be developed in both culmen and declive. There is a high lobus intermedius between the lobulus centralis and the first portion of the culmen. Its apex does not, however, reach the surface of the vermis superior. The general configuration of the culmen, when

distortion has been discounted, corresponds very closely to that depicted in Stilling's Fig. 122. The declive is also typical, though the sagittal section (Fig. 26) has, in this region, deviated somewhat from the median plane, so that the posterior part of the section passes through the edge of the hemisphere and not through the posterior part of the worm.

Other Parts of Vermis. The tuber, pyramis, uvula, and nodulus of the vermis inferior are present in the gross specimen in normal arrangement.

Hemisphæria Cerebelli. The hemispheres show no marked microscopic alterations.

Lobulus Quadrangularis. Counts of the *Randwülste* give the following result: Upper surface: Right side: 1. Near vermis, 21 (Stilling's normal, 17–19). 2. Near pons, 14 (Stilling's normal, 12–14). 3. In middle, between vermis and pons, 20 (Stilling's normal, 22–26). Left side: 1. Near vermis, 14 (Stilling). 2. Near pons, 15. 3. In middle, between vermis and pons, 23.

The six walls (*Wände*) correspond to the six *Wände* of the monticulus. The first wall is doubled on the left side; the second, on the right side. The fourth wall is but slightly developed, being represented by a projection in the depth between the third and fifth walls.

The dimensions of the lobulus quadrangularis are as follows on the upper surface: 1. In sagittal direction next to monticulus, left, 4.3 cm.; right, 4.6 cm. (Stilling, 33–40 mm.) Next to brachium pontis, left, 2.3 cm.; right, 2.4 cm. (Stilling, 18–20 mm.) 2. In transversal direction on anterior margin, left, 2.0 cm.; right, 2.4 cm. (Stilling, 28–35 mm.) On posterior margin, left, 5.8 cm.; right, 5.7 cm. (Stilling, 65–72 mm.)

Lobulus Semilunaris Superior. On the right side the number of *Randwülste* on the surface near the incisura cerebelli posterior is five; on the left side, seven. On the right side, on the surface in the middle, there are thirteen *Randwülste;* on the left side, fourteen.

The maximal sagittal measurement of the upper surface on the right side is 1.2 cm.; on the left side, 1.8 cm. The curved measurement transversally along the posterior margin is, on the right side 7.5 cm.; on the left side, 6.5 cm.

Lobulus Semilunaris Inferior. The number of *Randwülste* near vermis, right, 8 ; left, 10. Number of *Randwülste* near lateral margin, right, 4 ; left, 3. Number of *Randwülste* in middle, right, 8 ; left, 9. Maximal sagittal measures, right, 1.7 cm. ; left, 2.2 cm. Maximal length of posterior margin, right, 7.4 cm. ; left, 7.0 cm.

Lobulus Gracilis. Number of *Randwülste* near vermis, right, 5 ; left, 3. Number of *Randwülste* near lateral margin, right, 4 ; left, 3. Maximal sagittal measurement, right, 1.1 cm. ; left, 0.9 cm. Maximal sagittal measurement (curved), right, 6.9 cm. ; left, 6.0 cm.

Lobulus Biventer. Number of *Randwülste* in middle of inferior surface, right, 13 ; left, 12. Sagittal measurement, in middle, right, 3 cm. ; left, 2.9 cm. Length of posterior margin, right, 5 cm. ; left, 4.9 cm.

Flocculus. Number of *Randwülste* on inferior surface, right, 5 ; left (injured). Dimensions of inferior surface: right, 1.3×0.7 cm. ; left, 1.2×0.9 cm.

Tonsilla. On the left side the medial mass and lateral mass fuse as an acute angle. The lateral mass is 2.5 cm. long, the medial mass having the same measurement. There are nine *Randwülste* on the medial surface of the medial mass, and the same number on the lateral surface of the lateral mass.

On the right side the lateral mass measures 2 cm. in length ; the medial was the same. There are eight *Randwülste* on the medial surface of the medial mass, and seven on the lateral surface of the lateral mass.

Microscopic Examination of Case XX.

medulla spinalis. (Figs. 35, 45 and 46.)

Bloodvessels of the Spinal Cord. These were examined in section only. The bloodvessels found were compared with the descriptions of Adamkiewicz, Kadji, and Ross. The distribution of the larger vessels is normal. The tractus arteriosi spinalis anterior, anterolateralis, posterior, posterolateralis et lateralis are present. The larger veins are normal in number and distribution. The veins in the septum posterior of the thoracic portion of the cord are prominent. The finer vessels in the substantia grisea appear normal.

There is a noticeable increase in the number of Unna's plasma cells in the walls of the large bloodvessels within the substance of the cord, as well as in the vessels of the glia.

This is true of all portions of the cord, pars lumbalis, thoracalis et cervicalis.

Pars Lumbalis. The dimensions of the cord at the third lumbar segment, after formol hardening, are as follows: Anterior posterior diameter, 0.7 cm.; transverse diameter, 0.95 cm.

The areas of white and gray matter, measured by Professor Donaldson, are as follows: White matter, 8.870 cm.^{2}; gray matter, 3.583 cm.^{2} Ratio: 1 : 2, 3.

The anterior and posterior roots of the spinal nerves show no alteration, except possibly a slight increase in the endoneurium.

The pia mater is a little thickened. Thickness of pia over funiculus lateralis, 0.076 to 0.155 mm.; thickness of pia over funiculus posterior, 0.048 to 0.081 mm.; thickness of pia over funiculus anterior, 0.037 to 0.087 mm.

The subpial layer of neuroglia (*Gliahülle* of the Germans) is much thicker in the lumbar region than normal. The average thickness over the funiculus anterior is 0.48 mm. There are two triangular indentations in the anterior part of the cord where this glial layer measures 0.261 mm. and 0.243 mm. in depth. Thickness of subpial layer of glia over fasciculus Lissaueri, 0.152 mm.; thickness of subpial layer of glia over funiculus posterior (lateral part), 0.017 mm.; thickness of subpial layer of glia over funiculus posterior (near median septum), 0.094 mm.

Study of Sections Stained with Weigert's Myelin Sheath Stain or with Iron Hematoxylin Stain of Chromicized Tissues. The fasciculi stain, on the whole, normally. There are no degenerated areas. An exception is to be made for the middle root zone (Flechsig) of the funiculus posterior, which is lighter than the rest of the funiculus, and the glia is more abundant than normal in this lightened area. In view of the fact that the nucleus dorsalis and the direct cerebellar tract higher up are degenerated, it is interesting to note that it is this middle root zone of Flechsig in the lumbar cord which contains those posterior root fibers which run in to end in the gray matter of the nucleus dorsalis at a higher level. Aside from the alteration in this middle root zone, the dorsal funiculi show no

change. Lissauer's fasciculus is well developed. The pyramidal tracts and fasciculi proprii of the funiculus lateralis look normal. No alteration can be made out in the funiculus anterior. The fine medullated fibers (terminals and collaterals) which pass through the substantia gelatinosa appear normal in number and distribution. The anterior and posterior white commissures show no change.

Sections Stained by Nissl's Method in Thionin and in Toluidin Blue. The anterior horn cells are present in nearly normal number, though they may be slightly reduced. No change in size, shape, or distribution is discoverable. The internal morphology of these cells appears to be quite normal. The nuclei are centrally placed, and the nucleoli stain intensely. The stichochrome arrangement of the tigroid masses is well preserved in the dendrites and also in the perikaryons. Abundant masses of lipochrome can be seen in many of the anterior horn cells.

Pars Thoracalis. The cord has been a little flattened on removal. The dimensions are: Anterior posterior diameter, 0.5 mm.; transverse diameter, 0.9 mm.; average diameter in the two directions, 0.7 mm.

Professor Donaldson's measurements of a cross-section show an area of white matter of 6.955 cm.^{2} and an area of gray matter of 0.673 cm.^{2} This is a ratio of 1 : 13, which is clearly abnormal. (See Donaldson, H. H., and D. J. Davis. A description of chart showing the areas of the cross-sections of the human spinal cord at the level of each spinal nerve.[1])

The anterior and posterior roots of the spinal nerves show no changes.

The subpial layer of neurologia measures as follows: Thickness over funiculus lateralis (direct cerebellar tract), 0.35 mm.; thickness over funiculus anterior, 0.26 mm.; thickness over funiculus posterior (funiculus cuneatus), 0.35 mm.; thickness over funiculus posterior (funiculus gracilis), 0.22 mm.

Sections Stained with Weigert's Myelin Sheath Stain or with Iron Hematoxylin after Chromicizing. (Fig. 45.) *Funiculus Anterior.* Nothing abnormal discernible.

Funiculus Lateralis. The fasciculus spinocerebellaris dorsolateralis (direct cerebellar tract) is almost entirely degenerated. Through-

[1] Journal Comp. Nurol., Granville, 1903, vol. xiii. pp. 18–39.

out the whole thoracic portion of the spinal cord a narrow strip, situated on the dorsolateral surface of the cord, corresponding to the position of this tract, is almost devoid of medullated fibers, its place being represented only by glia. This area of degeneration does not extend farther forward, in the middle and lower portion of the thoracic cord at any rate, than a point opposite the columna intermediolateralis of the substantia grisea. It extends backward for a variable distance and usually does not reach as far behind as Lissauer's fasciculus. The internal margin of the degenerated stripe is irregular, corresponding to the admixture of the direct cerebellar tract with adjacent fiber systems (pyramidal tract). The external margin of the degenerated stripe is the periphery of the cord. Scattered medullated fibers still exist in the degenerated areas. These vary in diameter from 5 to 15 microns, the majority being large fibers (the average diameter of the fibers of the direct cerebellar tract is about 8μ).

The maximum depth of the degenerated area measured from the surface of the cord inward is on one side 0.315 mm. and on the other 0.560 mm. The degenerated area begins, as a rule, 1 mm. anterior to Lissauer's funiculus, and extends ventralward for a distance of 2.5 mm. The area is comma-shaped, the head of the comma being directed ventralward and the tail dorsalward.

The fasciculus spinocerebellaris ventrolateralis (Gowersi) shows no recognizable alterations, at least in the middle and lower thoracic cord. The fasciculi cerebrospinales laterales look normal, as do the fasciculi laterales proprii.

Funiculus Posterior. A light strip near the medial septum on each side, ventrally continuous with a much less lightened and very diffuse area in the lateral portion of the fasciculus cuneatus on each side, is visible. The glia is slightly increased in amount in this area. The areas correspond to the distribution of the third system of fibers (fœtus 35 cm. long) of Trepinski's developmental studies—that is, to precisely the same system of fibers as that to which belong the fibers of the middle root zone of the lumbar portion of the spinal cord. Otherwise the funiculi posteriores show no alterations.

Sections Stained by Nissl's Method in Thionin and in Toluidin Blue. Sections were taken from ten different levels of the pars thoracalis. The whole cord is flattened anteroposteriorly, possibly

owing to slight injury on removal. With this flattening there is marked displacement of the posterior horns to the side. The anterior horn cells are present in normal numbers, are of the usual size, and present the typical stichochrome arrangement of their tigroid masses.

The cells of the columna intermediolateralis are a striking feature of the sections throughout the pars thoracalis, and they are present in normal numbers, are elliptical usually in shape, and measure from 7μ to 38μ in the long diameter and from 5μ to 18μ in the short diameter (Ziehen gives as the normal 12μ to 15μ in the long and 5μ to 15μ in the short axis). The tigroid substance in these cells is very variable. The masses are irregular in size, shape, and distribution. In many of the cells the tigroid masses are arranged at the periphery, the center of the cell being pale or staining diffusely blue. The nuclei of some of these cells are situated at one pole or one edge of the cell; they may have a crescentic shape and look shrunken.

The cells of the columna posterior include (1) the cells of the nucleus dorsalis (Clarke's column); (2) the cells of the substantia gelatinosa Rolandi; (3) the cells of the zonal layer (*cellules limitantes*), and (4) the cells of the columna posterior propria (Waldeyer's nucleus of the dorsal horn).

Of these, the cells of Clarke's column interest us most, for they have almost entirely disappeared throughout the whole length of the nucleus. In many sections not a single cell is visible; where any cells are left at all, the number does not exceed from one to three in a section. (Fig. 35.) The few cells remaining present no characteristic alterations when compared with the normal cells of control preparations. The tigroid masses are irregular in size and distribution; occasionally they are peripherally disposed. The nuclei may be eccentrically placed, and the nucleoli stain intensely.

An examination of the so-called Gierke's cells of the substantia gelatinosa has been made. On comparison with control preparations they appear to be normal.

The marginal cells of the zonal layer are normal in number and appearance. I cannot detect any alteration in the triangular cells of Waldeyer's nucleus of the dorsal horn.

Pars Cervicalis and Transition into Medulla. *Sections Stained with Weigert's Method and with Iron Hematoxylin.* The

degenerated area still corresponds to the situation of the direct cerebellar tract. The area is larger than in the thoracic portion of the cord, and begins nearer the dorsal horn. In sections through the junction of the spinal cord with the medulla oblongata the degenerated area is exquisitely marked out. It is approximately triangular in shape, the apex of the triangle being on the surface, behind, opposite the dorsal horn, the base in front The two sides of the triangle are formed by the periphery of the cord and the lateral surface of the lateral pyramidal tract, respectively. On one side of the cord a large bundle of pyramidal tract fibers plunges directly through the degenerated area, just after decussation ; these fibers are surrounded on all sides by the pale-yellow glia of that part of the cord from which fibers of the direct cerebellar tract have almost entirely disappeared (*vide* Fig. 41). The distance from the apex to the base of the triangle is 2.128 mm. ; the width of the base is 0.598 mm. A few scattered healthy fibers remain in the degenerated area, as was the case in the sections through the pars thoracalis. These are chiefly fibers of very large caliber. The subpial neuroglia layer over the degenerated area measures 0.113 mm. in thickness.

There is slight diffuse lightening of the area extending for 1 mm. to 1.5 mm. in front of the main triangle of degeneration, and with the high power it is seen that the nerve fibers do not stand so closely together here as they do normally. Either a few fibers of the direct cerebellar tract have been present in this area or we have to deal with a slight loss of fibers in the ventral spinocerebellar tract of Gowers.

In the dorsal funiculi there is a long, narrow, slightly lightened strip close to the medial margin of the fasciculus gracilis, and a still more diffuse, slightly lightened area near the lateral middle portion of the fasciculus cuneatus. There has been an actual loss of fibers from these areas.

The fasciculi cerebrospinales contain no lightened areas in the cross-sections. This is true, also, of the various fasciculi proprii. Helweg's path is not distinguishable by any color differences from the surrounding white matter.

Sections Stained with Nissl's Method with Thionin and with Toluidin Blue. The cells of the ventral horns are present in normal

number and distribution. The tigroid substance is abundant, and a large number of these cells are richly provided with masses of lipochrome. No alteration in any of the nerve cells in this portion of the nervous system is discernible.

MEDULLA OBLONGATA. (Figs. 38, 39, 40 and 41.)

LEVEL OF DISTAL PORTION (ABOVE DECUSSATIO PYRAMIDUM AND AT THE LOWER PART OF THE DECUSSATIO LEMNISCORUM, CENTRAL CANAL STILL CLOSED). *Sections Stained with Weigert's Myelin Sheath Stain or with Iron Hematoxylin.* There is a triangular area of degeneration in the position of the direct cerebellar tract which is situated, at this level, just ventrolateral from the laterally deflected dorsal horn on each side. The apex of the triangle is directed medialward; the base, somewhat curved, corresponds to the periphery of the medulla. Between the apex of the triangle and the most ventral portion of the substantia gelatinosa, an area, 0.25 mm. in breadth, of undegenerated, rather fine fibers, intervenes. On the very periphery of the medulla the area of degeneration is bounded by some medullated fibræ arcuatæ externæ.

The funiculi posteriores are normal in appearance, as are the pyramids and the bundles in the regions of the medulla other than that of the direct cerebellar tract The spinal tract of the trigeminal nerve looks normal.

LEVEL OF NUCLEUS NERVI HYPOGLOSSI AND NUCLEUS ALÆ CINEREÆ. *Sections Stained with Weigert's Method.* The pyramids and stratum interolivare lemnisci are normal on each side. The fibræ arcuatæ internæ and fibræ arcuatæ externæ appear normal. The tractus spinalis n. trigemini and the fasciculus solitarius are well developed and unaltered.

The degenerated area corresponding to the direct cerebellar tract has disappeared at this level, apparently having turned into the corpus restiforme. The latter structure, however, appears to be evenly dark and the position of the degenerated fibers is not ascertainable. The root fibers of the nervus hypoglossus look normal. The fibræ olivocerebellares show no obvious change. No extensive alterations have been made out in the various masses of gray matter at this level—nucleus nervi hypoglossi, nucleus alæ cinereæ, nucleus

olivaris inferior, nuclei olivares accessorii, nucleus funiculi cuneati, and nuclei arcuati. The number of cells in the gray matter of the olive is probably smaller than normal; indeed, the size of all the structures seems somewhat diminished. (See Fig. 33.)

Level of Proximal Extremity of the Medulla Oblongata at Region of Entrance of N. Acusticus. *Sections Stained with Weigert's Preparations.* No alterations are visible in the vestibular nerve or its nuclei.

pons varolii.

Level of Brachium Conjunctivum and Velum Medullare Anterius. The brachium conjunctivum is smaller in volume than normal; the fibers are a little thinned; the average caliber of the fibers is small; the glia is rather more abundant than normal. The fasciculus longitudinalis medialis, though rather small in volume, in transverse section stains normally. There is no degeneration of the lemniscus lateralis. The fasciculus tegmenti centralis (*centrale Haubenbahn*) is of normal size and stains well. The longitudinal fasciculi and the transverse fibers of the pons stain normally. The gray matter of the formatio reticularis in the pars dorsalis pontis and that of the nuclei pontis in the pars ventralis appear to be normal in amount and distribution.

cerebellum. (*Weigert Preparations.*)

Study of Sagittal Sections through Cerebellum. 1. *Sagittal Sections Near Median Plane of Vermis.* (Fig. 26.)

(*a*) *Corpus Medullare.* The laminæ medullares look normal in Weigert preparations. In the corpus trapezoideum and the main vertical limb of the arbor vitæ the transversely running fibers of the great anterior decussation are to be seen.

(*b*) *Substantia Corticalis.* Except that the vermis is on the whole somewhat smaller than in the brother's brain, the appearances are very much the same. The molecular layer is separated from the granular layer by the layer of ganglion cells. The latter are very irregularly distributed, but this is true of the normal cerebellum.

(*c*) *Nucleus Fastigii.* The area for this nucleus is present in its normal position, but the study of a number of sections shows an

apparent diminution in the number of nerve cells present in it. The nerve cells found are smaller than normal. Glia cells are abundant. The medullated fibers extending through the brachium conjunctivum between the region of Deiters' nucleus in the medulla and the region of the nucleus of the roof are a prominent feature of the sections; they are present in apparently normal numbers.

2. *Sagittal Section About* $6\frac{1}{2}$ *mm. or* 7 *mm. Lateral from the Median Plane.* The section passes through the nucleus globosus and the nucleus emboliformis and through the medial portion of the hemisphærium cerebelli, thus cutting, above, the lobulus quadrangularis and the lobulus semilunaris superior, and below, the lobulus semilunaris inferior, the lobulus gracilis, the pyramis, and the tonsilla.

(*a*) *Substantia Corticalis.* No alterations are discernible.

(*b*) *Nucleus Emboliformis.* In this section this nucleus is spindle-shaped, the maximum length of the spindle being 8 mm., its maximum dorsoventral diameter $2\frac{1}{4}$ mm.; above it are three minute islands of gray matter, which belong to the most medial part of the nucleus dentatus, while below and behind it is the mushroom-like head of the nucleus globosus. Beneath it and in front of it are the fibers of the brachium conjunctivum. The section evidently passes through only the more lateral and posterior part of the nucleus emboliformis. Large numbers of large ganglion cells are present.

(*c*) *Nucleus Globosus.* This section passes through the posterior head of the mushroom-like nucleus and through the posterior part of its stem. Greatest vertical diameter in sections equal 2 mm.; greatest sagittal diameter in sections equal $5\frac{1}{2}$ mm.

Owing to the flattening of the cerebellum as a whole in the hardening process, it is probable that the vertical diameter is here very small owing to an increase in the transversal diameter. The nucleus globosus is separated from the under surface of the nucleus emboliformis by a well-preserved narrow band of medullated fibers. Numbers of ganglion cells are present in the nucleus.

(*d*) *Nucleus Dentatus.* Only three small islands of ganglion cells are present; these are obviously cross-sections through the most medial projections of the dentate nucleus.

(*e*) *Corpus Medullare.* The laminæ medullares of the different cortical areas are well developed and fuse with the central white

substance. The transversely and obliquely cut fibers corresponding to the anterior and posterior decussation commissures look normal. The fibers of the brachium conjunctivum (Stilling's processus cerebelli ad corpora quadrigemina) look a little thinner and the blood-vessels in it are dilated.

3. *Sagittal Section through Hemisphærium Cerebelli about* 14 *mm. Lateral from Sagittal Median Plane of Vermis.* The section passes through the lobus quadrangularis, lobulus semilunaris superior, lobulus semilunaris inferior, lobulus gracilis, lobus biventer and the flocculus, the lateral part of the nucleus dentatus, the fibræ semicirculares cerebelli, and the central part of the brachium pontis.

The nucleus dentatus is here growing small in size and is much convoluted. The cells in its gray matter are more numerous than in the nucleus dentatus of the brother, but less numerous than in a normal control. Each cell contains a mass of yellowish-green pigment (in toluidin-blue preparations) which is probably identical with the lipochrome of anterior horn cells. I can make out no decided alterations in the corpus medullare at this plane.

4. *Sagittal Sections through Hemisphærium Cerebelli Lateral from the Nucleus Dentatus.* The corpus medullare gradually grows smaller in volume, the fibræ semicirculares less distinct as in normal preparations. No alterations other than the general diminution in volume are discernible.

Study of Frontal Sections through Cerebellum. 1. *Frontal Section a Few Millimeters in Front of Apex of Culmen.* This section passes in front of all the gray nuclei of the cerebellum and shows, besides the cortical portions of the vermis and hemisphærium, the great central mass of white matter just as it is going over into the brachium pontis. No areas of degeneration are visible.

2. *Frontal Section Near Apex of Culmen.* The section has passed a little obliquely lateralward and backward, having caught the jagged edge of the lateroinferior portion of the anterior extremity of the nucleus dentatus. The mass of fibers corresponding to the area of the brachium conjunctivum looks thin and lightened in Weigert preparations, though it is crossed by obliquely cut strands of deeply staining fibers of large caliber. The latter accumulate near the nucleus fastigii. The latter is not well developed, and relatively few cells are to be found in it.

3. *Frontal Section about 6 mm. Behind Highest Point of Culmen.* The origin of this section is easily recognizable by the horseshoe-shape presented by frontal sections of the nucleus emboliformis in this plane. Below it is a cross-section of the nucleus globosus, here represented by a large, rather triangular mass with two small gray masses lateral from it and one small gray mass just medial from it. All these lie in the hilus nuclei dentati. The only representative of the nucleus fastigii is a minute mass of gray matter near the median plane of the vermis.

The white matter within the nucleus dentatus looks pale in Weigert preparations, and the bloodvessels are dilated. This pallor is not so marked, however, as in the brain of the brother.

The great anterior decussation commissure is well developed and stains intensely in the Weigert preparations.

4. *Frontal Section through the Declive and Posterior Extremity of the Nucleus Dentatus.* Sections through this level show the most posterior portions of the nucleus dentatus embedded in the corpus medullare. Sections through the nucleus dentatus when compared with sections from the normal cerebellum reveal a smaller number of nerve cells.

Nissl Preparations.

Sections were made from the cortex of the vermis and of the cerebellar hemispheres. No striking differences in appearance in the sections from the two sources could be made out, except that the Purkinje cells in the hemisphere look smaller than in the vermis. (See Figs. 28 and 29.)

The *molecular layer* measures from 0.326 mm. to 0.363 mm. in thickness. It is thicker near the bases than at the summits of the folii.

The *granular layer* measures 0.4 mm. in thickness at its thickest part. It is, however, very variable in depth and near the bottom of the interlamellar sulcus may be as thin as 0.1 mm. These measurements are smaller than those given as normal by Poirier et Charpy, according to whom the molecular and granular layers are of equal thickness, each measuring 0.5 mm. in depth. Von Kolliker, however, gives as the normal thickness of the melecular layer in human beings the measurements 0.15–0.40 mm. ; he does not make any statement regarding the thickness of the granular layer.

The Purkinje cells are of normal size in the vermis, but rather small in the hemisphere ; they present cell bodies rich in stainable substance of Nissl, large, pale nuclei, and large, deeply staining nucleoli. The question, "Are the Purkinje cells present in normal numbers?" is a difficult one to answer. They often lie very close together in the single row in which they are arranged, but wide gaps between Purkinje cells are very frequently met with (*vide* Fig. 29). These gaps may be as wide as 0.6 mm. Stilling's statement with regard to the distances between the individual Purkinje cells is as follows :

"Die grossen Nervenzellen liegen nämlich, in mehr oder minder regelmässiger Weise, in mehr oder minder grossen Strecken von einander entfernt, und lassen also einen Zwischenraum, meist je von 1/50‴, zwischen sich ; oft stehen sie auch gedrängter in einer und derselben Ebene, nur durch eine Entfernung je von 1/150‴ getrennt; nicht selten berühren sich sogar mehrere unmittelbar. In manchen Ebenen sind sie dagegen wieder auffallend weit, bis zu 1/12‴, von einander entfernt. Da man in seinen Abschnitten doch meist nur Theile der einzelnen grossen Nervenzellen (mutilirte) zu Gesicht bekommt, so übersicht man gewiss oft genug Fragmente dieser Nervenzellen, und wo eine auffallend lange Strecke ohne grosse Nervenzellen erscheint, lagen vielleicht dennoch einige, die durch die Präparation unkenntlich wurden. Immerhin aber treten in den, zwischen den einzelnen grossen Nervenzellen befindlichen, grösseren oder kleineren Zwschenräumen dennoch die einzelnen Elemente der Zellen- und Körnerschicht in unmittelbare Berührung resp. Verbindung. d. h. an zahllosen Stellen."

If he had dealt with thinner sections he would doubtless have met with instances of greater intervals, but even allowing for the difference in thickness of sections, it would seem not unlikely that there is in the case here described an actual diminution in the total number of Purkinje cells as compared with Stilling's findings. On comparison with control preparations, however, I am not convinced that the number of Purkinje cells is below normal. In Fig. 27 has been reproduced a section of the hemisphere of the cerebellum of a physician dead of myasthenia gravis, in which disease there is presumably no diminution in the number of Purkinje cells. The interspaces between cells are seen to be very large.

In Krohm's[1] case of atrophy of the cerebellum, met with in an ataxic cat, studied in Donaldson's laboratory, there was extensive atrophy of the cerebellum as a whole, with marked diminution in thickness, particularly of the molecular layer. In places the Purkinje cells had disappeared entirely, leaving open, empty spaces in their places, and the Purkinje cells in general were markedly shrunken. There seemed to be but little alteration in the granular layer or in the white medullary substance.

Cerebral Cortex. *Gyrus Centralis Anterior.* The gray matter is 2 mm. thick on the surface, 2.5 mm. to 3 mm. thick on the walls of the sulci. The plexiform layer measures 0.319 mm. in thickness. The various layers of pyramidal cells are present in Nissl preparations. I can make out no definite alterations in them.

Gyrus Cuneus (Near Fissura Calcarina), Nissl Preparations. The plexiform layer measures 0.156 mm. in depth. It contains a very few scattered nuclei, the majority being small and round and looking like ordinary glia nuclei. A few polygonal and spindle-shaped nuclei are, however, also present in this layer. The layer of small pyramidal cells and the layer of medium-sized pyramidal cells together measure 0.438 mm. in depth. The layer of large stellate cells is 0.133 mm. deep; that of the small stellate cells, 0.292 mm.; and that of the small pyramidal cells, with ascending axones, 0.119 mm. deep. The giant pyramidal cells are widely removed from one another and their cell bodes and nuclei look normal. The layer of pyramidal cells, with curved, ascending axones, measures 0.199 mm. in depth, and the layer of spindle-shaped cells 0.20 mm. The total thickness of the gray matter here is 1.6 mm. in its thinnest part.

Résumé of Morbid Anatomy.

The brains and cords of both cases are relatively small, the cords, medulla, and pons in each case looking smaller in proportion than the cerebrum.

The cerebral cortex in both cases is well fissured; indeed, if there be abnormality, it is on the side of overfissuration rather than on that of underfissuration. The form of the various sulci and gyri

[1] Atrophy of Cerebellum in a Cat, Journal of Nervous and Mental Diseases, New York, October, 1892.

is fully described in the protocols, and a study of these reveals no deviations from the normal type which can be regarded as standing in relation to the disease from which the family suffered. The cerebral topography is, however, interesting, aside from the pathology of the case, in that it presents an opportunity for comparing the similarities and differences in the brain surfaces of two brothers.

The cerebellum, though a little small in each case, is very typical in macroscopic configuration. The cerebellar peduncles (superior, middle, and inferior) are all relatively small; the diminution in size is not marked, however.

The spinal cord looks a little smaller than normal in each case, that of Case XVIII. looking smaller than that of Case XX., and this is in accord with the actual measurements. Measurements made by Professor Donaldson show an abnormal ratio between the area of white matter and the area of gray matter in the cross-sections.

The microscopic study in both cases reveals marked degeneration in the gray and white matter of the spinal cord, medulla oblongata, and cerebellum. The degeneration is considerably more advanced in Case XVIII. than in Case XX., though the difference is in degree rather than in kind. The degeneration involves in both cases chiefly nerve cells and nerve fibers of centripetal paths, including one system of exogenous fibers of the posterior funiculus (apparently corresponding to the third fœtal system of Trepinski), the dorsal nucleus of Clarke, the direct cerebellar tract of Flechsig in the lateral funiculus and its continuation in the restiform body. In these structures the degeneration is very extensive; in addition there has been some involvement of the dentate nucleus of the cerebellum and the brachium conjunctivum, and probably also of the inferior olivary nucleus of the medulla oblongata; in the more advanced case there may be slight diminution in the number of the anterior horn cells, and of the fibers of the nerve roots.

Corresponding to the degeneration in the white fibers of the spinal cord there has been an increase in the glia tissue—an increase which is relatively more pronounced in the dorsal funiculus than in the area of the lateral funiculus corresponding to the direct cerebellar tract.

Only one case from this family has been previously studied

histologically, but that one, fortunately, by Dr. Adolf Meyer,[1] who found no circumscribed cerebellar lesion, but made out a marked diminution in the number of cells in Clarke's nucleus, a degeneration of the direct cerebellar tract, and an elective degeneration of the posterior funiculus, especially marked in the pars cervicalis, where it involved the medial part of the fasciculus gracilis, and to a less extent the posterior part of this fasciculus and the most medial part of the fasciculus cuneatus.

In general, then, the lesions in the three cases thus far studied are nearly identical as regards the neurones involved, though there are differences in the extent of the process quite in accord with the differences in clinical symptoms as the cases were more or less advanced. Dr. Meyer interprets the degeneration in the posterior funiculus as a degeneration of the collaterals which connect the lower levels with the higher (cerebral and cerebellar) apparatus, comparable to the degeneration of the lateral pyramidal tracts of the lower segments of the cord where the basilar part of the cerebral peduncle and the pyramids of the medulla show no degeneration. I am inclined to look upon the degeneration in the posterior funiculus rather as systemic—*i. e.*, as involving certain only of the stem fibers and collaterals of the intramedullary continuation of the posterior roots, namely, those corresponding to one period of medullation in the embryo. Recent studies make it appear probable (1) that the medullation of the fibers of the posterior roots corresponds more or less closely to the medullation of their intrafunicular continuations, and (2) that the fibers of the posterior funiculi which terminate in the nucleus dorsalis are terminals of the main ascending limb of bifurcation rather than collaterals. In the near future the writer hopes, in another paper, to enter into a rather full discussion of the relation of the lesions found in these cases to the clinical symptoms presented by the patients during life, a discussion which necessarily involves some consideration of the whole question of co-ordination. The discussion of the relations of the disease to Friedreich's ataxia and similar maladies and of the validity of Marie's[2] classification of hereditary cerebellar ataxia is also deferred. It will be of special interest to contrast the Haud family studied clinically by Klippel

[1] The Morbid Anatomy of a Case of Hereditary Ataxia, Brain, 1897, vol. xx. pp. 276–288.
[2] Sur l'hérédo-atakie cérébelleuse, Semaine méd., Paris, 1893, vol. xiii. pp. 444–47.

and Durante and anatomically by Thomas and Roux with the cases described above. In the French family the lesion involved chiefly the ventrolateral cerebellar tract of Gowers. Meyer's studies and my own show that in the American family described by Sanger Brown the dorsolateral cerebellar tract is the one which degenerates. The present report, together with that of Dr. Adolf Meyer, makes it very clear that the morbid anatomy of the affected members of the family described by Dr. Sanger Brown presents very constant features; we now know with certainty the neurone systems principally involved in the individuals who are affected, though we are as yet entirely ignorant as to why just these neurone systems should be picked out.

DISCUSSION.

Dr. Starr: It seems to me this communication is of extreme interest, not only from a neurologic standpoint, in aiding the diagnosis of this type of ataxia, but in another way, as throwing a great deal of light upon our knowledge of the physiology of the muscular sense. This observation establishes conclusively that there are two independent and separate nervous systems controlling the muscular sense; that one is connected with the balancing power of the body, and is the system here diseased, the system going to the Clarke cells, and by the direct cerebellar tracts to the nuclei in the cerebellum; and the second is related to the elements of the muscular sense, which guide voluntary movement.

In the term "ataxia" we have included symptoms due to a lesion of these two systems, and have not distinguished between them. In ataxia we must now distinguish between the elements of the cerebellum and the elements of the muscular sense that guide voluntary movement. The doctor called attention among the clinical features of these cases, that there was no disturbance of the so-called muscular sense. The system that controls that sense passes up through the fasciculi cuneati, interolivary tract, and lemniscus up to the thalamus, and thence to the cortex, and this was not involved here. The cases proved that it is independent of the system going to the cerebellum.

This paper also throws light incidentally upon a point of treatment. We know that in locomotor ataxia we can get a marked improvement—get our patients walking around, if they are trained properly in the movements of voluntary adjustment, guided by a certain amount of voluntary activity, which takes the place of the automatic acts when these are defective. Thus in locomotor ataxia, when the second system controlling muscular sense is defective, we can call into play the activity of voluntary centers used by the second system controlling muscular sense.

INDEX.

Abbott, A. C., the action of alcohol in disease, 425
the adrenal gland and its active principle in their relations to cytolysins and antitoxin production, 275
Acetone, formation and excretion of, 260
Actinomycosis of the central nervous system, 427
Address of the President, 1
Adrenal gland and its active principle in their relations to cytolysins and antitoxin production, 275
Alcohol in disease, studies on the action of, 391, 402
in infections, 391, 402
Anemia, splenic, 522
Artificial immunity in experimental tuberculosis, 97
Ataxia, hereditary, 637
Autolysis in lobar and unresolved pneumonia, 359

Bacterial cells, a further report on the study of, 365
Banti's disease, 522
Barker, Lewellys F., a description of the brains and spinal cords of two brothers dead of hereditary ataxia, 637
Bathycardia, 5
Bentz, Charles A., experimental studies on the eosinophilia of trichinosis, 152
Blumer, George, case of chronic lymphatic leukemia without enlargement of the lymph nodes, 378
sudden death in early life, 253
Bovine tuberculosis, transmission of, by milk, 9
Bridge, Norman, chronic cyanosis, 322
intussusception, 85
Bulbar paralysis, acute, due to hemorrhage and softening of the pons and medulla, 446

Cabot, Richard C., an experimental study of nephrotoxins, 596
chronic cyanosis, 318, 325
splenic anemia, 552
studies on the action of alcohol in disease, especially upon the circulation, 402, 426
Cancer of the lung, 625

Capsule of kidney, studies upon, 192
Cardiopulmonary murmur, clinical associations and significance of, 157
Chronic lymphatic leukemia, 378
Cirrhosis, 522
Clinical associations and significance of the cardiopulmonary murmur, 157
Cohen, S. Solis, chronic cyanosis, 324
Cutler, E. G., decapsulation of the kidney, 357
Cyanosis, chronic, with polycythemia and enlarged spleen, 299

Dana, Charles L., acute bulbar paralysis due to hemorrhage and softening of the pons and medulla, 446
Decapsulation of the kidney for chronic parenchymatous nephritis, 347
Delafield, Francis, post-typhoid sepsis, 326
Dermatomyositis, 184
Description of the brains and spinal cords of two brothers dead of hereditary ataxia, 637
Dock, George, a clinical and pathological study of two cases of splenic anemia, with early and late stages of cirrhosis (early and late stages of Banti's disease), 522, 555
the action of alcohol in disease, 426
Drake, Arthur K., case of extreme malformation of the heart, 272

Edebohls' operation for decapsulation of the kidney, 347
Emerson, Haven, studies upon the capsule of the kidney, 192
Eosinophilia of trichinosis, studies on, 153
Erythema group of skin diseases, visceral manifestations of, 599
Experimental studies on the eosinophilia of trichinosis, 152
study of nephrotoxins, 557
Experiments to determine whether alcohol does good in infections by increasing the bacteriolytic power of the blood, 391
Extreme malformation of the heart, 272

Flexner, Simon, a note on autolysis in lobar and unresolved pneumonia, 359, 364
an experimental study of nephrotoxins, 597
Forchheimer, F., dermatomyositis, 184
Frazier, Charles H., report of a case of decapsulation of the kidney (Edebohls' operation) for chronic parenchymatous nephritis, 347
Fussell, M. H., splenic anemia, 554

Gastric syphilis, case of, 176
Gonococcal peritonitis, two cases of, 202
Gordinier, Hermon C., case of chronic lymphatic leukemia without enlargement of the lymph nodes, 378
Griffith, J. P. Crozer, sudden death and unexpected death in early life, with especial reference to the so-called thymus death, 235

Hare, H. A., chronic cyanosis, 322
pulmonary note on some experiments to determine whether alcohol does good in infections by increasing the bacteriolytic power of the blood, 391
Heart, extreme malformation of, 272
Hektoen, Ludvig, note on typhoid fever and scarlet fever, with special reference to the diagnostic value of blood cultures, 254
Hematinuria, paroxysmal, 54
Hémoglobinurie a frigore, 54
Hemorrhagic infarction of the lung, 337
Henry, Frederick P., pulsating serous pleural effusion, 336
report of a case of pulsating empyema necessitatis, with three strongly pulsating tumors, 71
Hereditary ataxia, 637
Herrick, J. B., splenic anemia, 553
Howard, William Travis, actinomycosis of the central nervous system, 427

Infantile scorbutus, 180
Influence of the different varieties of fat on the formation and excretion of acetone, 260
Intussusception, 85

Jacobi, A., autolysis in lobar and unresolved pneumonia, 364
gonococcal peritonitis, 206
infantile scorbutus, 183
skin lesions associated with rapid growth of long bones, 201
sudden death in early life, 253
the action of alcohol in disease, 424
Janeway, E. G., bathycardia, 5, 8
skin lesions associated with rapid growth of long bones, 201
Joslin, E. P., chronic cyanosis, 323
the influence of the different varieties of fat on the formation and excretion of acetone, 260

Kelly, A. O. J., acute lymphocytic leukemia, with reference to its myelogenous origin, 481
splenic anemia, 555
Kidney, capsule of, studies upon, 192
decapsulation of, for chronic parenchymatous nephritis, 347
Kinnicutt, Francis P., gonococcal peritonitis, 206
splenic anemia, 555
Kober, George M., the transmission of bovine tuberculosis by milk, 9
Koplik, Henry, post-typhoid sepsis, 332
tuberculosis of the tonsils and the tonsils as a portal of tuberculous infection, 262

Lafleur, H. A., a case of gastric syphilis, 176
Les vergetures de croissance, Jules Comby, 197
Leukemia, acute lymphatic, 481
Lineæ albicantes, 197
Lung, primary cancer of, 625
Lymphatic leukemia, acute, 481
chronic, 378

McCrae, John, typhoid fever, 165
McPhedran, Alexander, bathycardia, 8
case of massive hemorrhagic infarction of the lung, due to pulmonary endarteritis and thrombosis, 337
case of pulsating serous pleural effusion, 334
chronic cyanosis, 321
decapsulation of the kidney, 357
MacCallum, W. G., an experimental study of nephrotoxins, 598
on the production of specific cytolytic sera for thyroid and parathyroid, with observations on the physiology and pathology of the parathyroid gland, especially in its relation to exophthalmic goitre, 35
Mackenzie, J. J., case of massive hemorrhagic infarction of the lung, due to pulmonary endarteritis and thrombosis, 337
Mammalian tubercle bacilli III., studies in, 109
Massive hemorrhagic infarction of the lung, due to pulmonary endarteritis and thrombosis, 337
Meltzer, S. J., autolysis in lobar and unresolved pneumonia, 364
studies upon the capsule of the kidney, 192
Migraine, treatment of, 368
Morse, John Lovett, the relation of chronic enlargement of the spleen to anemia in infancy, 207
Musser, John H., primary cancer of the lung, 625
the action of alcohol in disease, 426

Nephrotoxins, an experimental study of, 557
Northrup, W. P., skin lesions associated with rapid growth of long bones, 197
two cases of general gonococcal peritonitis in young girls under puberty, 202, 206

Osler, William, bathycardia, 7
chronic cyanosis, with polycythemia and enlarged spleen; a new clinical entity, 299, 325
splenic anemia, 554
of infancy, 234
studies in mammalian tubercle bacilli III., 151
skin lesions associated with rapid growth of long bones, 201
visceral manifestations of the erythema group of skin diseases, 599

Paroxysmal hematinuria, 54
Peabody, George L., post-typhoid sepsis, 332
splenic anemia, 553
Pearce, Richard M., an experimental study of nephrotoxins, 557, 598
Peritonitis, gonococcal, two cases of, 202
Post-typhoid sepsis, 326
President's address, 1
Presystolic mitral murmur, case of, 81
Primary cancer of the lung, 625
Production of specific cytolytic sera for thyroid and parathyroid, with observations on the physiology and pathology of the parathyroid gland, especially in its relation to exophthalmic goiter, 35
Pulmonary endarteritis and thrombosis, 337
Pulsating empyema necessitatis, with three strongly pulsating tumors, 71
serous pleural effusion, case of, 334
Putnam, James J., the clinical associations and significance of the cardiopulmonary murmur, 157

Rachford, B. K., treatment of migraine, 368
Relation of chronic enlargement of the spleen to anemia in infancy, 207
Robinson, Beverley, post-typhoid sepsis, 333
Rotch, Thomas Morgan, infantile scorbutus, 180, 183

Scarlet fever, note on, 254
Scorbutus, infantile, 180
Sepsis, post-typhoid, 326
Sewall, Henry, an experimental study of nephrotoxins, 597
Shattuck, F. C., chronic cyanosis, 320, 325
the action of alcohol in disease, 425
Skin diseases, visceral manifestations of the erythema group of, 599
lesions associated with rapid growth of long bones, 197
Smith, Theobald, studies in mammalian tubercle bacilli III., 109, 151
transmission of bovine tuberculosis by milk, 34
Splenic anemia, 522
of infancy, 207
Starr, M. Allen, hereditary ataxia, 709
Stengel, Alfred, chronic cyanosis, 322
Stewart, James, address of the President, 1
Stockton, C. G., chronic cyanosis, 321
Studies in mammalian tubercle bacilli III., 109
upon the capsule of the kidney, 192
Sudden death and unexpected death in early life, with especial reference to the so-called thymus death, 235
Syphilis, gastric, case of, 176

THIRD and final report of a case of presystolic mitral murmur, complicating pregnancy, etc., with exhibition of specimen, showing triple valvular lesion, 81
Thompson, W. Gilman, paroxysmal hematinuria, 54
Transmission of bovine tuberculosis by milk, 9
Trudeau, Edward L., artificial immunity in experimental tuberculosis, 97
transmission of bovine tuberculosis by milk, 34
Tuberculosis, artificial immunity in experimental, 97
of the tonsils and the tonsils as a portal of tuberculous infection, 262
Typhoid fever, 165, 253
Tyson, James, report of a case of decapsulation of the kidney (Edebohls' operation) for chronic parenchymatous nephritis, 347
the third and final report of a case of presystolic mitral murmur, complicating pregnancy, etc., with exhibition of specimen, showing triple valvular lesion, 81

VAUGHAN, VICTOR C., a further report on the study of bacterial cells, 365
Visceral manifestations of the erythema group of skin diseases, 599

WARTHIN, ALDRED SCOTT, a clinical and pathological study of two cases of splenic anemia, with early and late stages of cirrhosis (early and late stages of Banti's disease), 522, 556
Welch, W. H., splenic anemia, 554
the action of alcohol in disease, 423
Williams, Francis H., bathycardia, 7
the use of the X-rays in the treatment of diseases of the skin, of new-growths, of the glandular system, and of other diseases, and as a means of relieving pain, 89
Williams, Herbert U., experimental studies on the eosinophilia of trichinosis, 152
Wright, James Homer, case of extreme malformation of the heart, 272

X-RAYS, use of, in the treatment of diseases of the skin, of new-growths, of the glandular system, and of other diseases, and as a means of relieving pain, 89